SEARCH HISTORY

=> d his ful

(FILE 'HOME' ENTERED AT 15:11:25 ON 28 SEP 2006)

FILE 'HCAPLUS' ENTERED AT 15:11:33 ON 28 SEP 2006
E MEDICHERLA SATYANARAYANA/AU
L1 29 SEA ABB=ON ("MEDICHERLA SATYA"/AU OR "MEDICHERLA SATYANANYANA" /AU OR "MEDICHERLA SATYANARAYANA"/AU)
E PROTTER ANDREW A/AU
L2 73 SEA ABB=ON ("PROTTER A A"/AU OR "PROTTER ANDREW"/AU OR "PROTTER ANDREW A"/AU OR "PROTTER ANDREW ASHER"/AU OR "PROTTER ANDY"/AU)
E SCHREINER GEORGE F/AU
L3 170 SEA ABB=ON ("SCHREINER GEORGE"/AU OR "SCHREINER GEORGE E"/AU OR "SCHREINER GEORGE F"/AU OR "SCHREINER GEORGE FREDERIC"/AU)
L4 5 SEA ABB=ON L1 AND L2 AND L3
L5 3 SEA ABB=ON L4 AND ?DIABETES?
SELECT RN L5 1-3

FILE 'REGISTRY' ENTERED AT 15:13:00 ON 28 SEP 2006
L6 22 SEA ABB=ON (165245-96-5/BI OR 50-99-7/BI OR 9004-10-8/BI OR 152060-53-2/BI OR 1670-87-7/BI OR 176023-64-6/BI OR 179800-23-8 /BI OR 192333-55-4/BI OR 253-82-7/BI OR 309913-28-8/BI OR 309913-29-9/BI OR 309913-41-5/BI OR 309913-51-7/BI OR 309913-59 -5/BI OR 309913-92-6/BI OR 309914-09-8/BI OR 309914-17-8/BI OR 309914-25-8/BI OR 309914-66-7/BI OR 309914-79-2/BI OR 309914-94 -1/BI OR 627536-09-8/BI)

FILE 'HCAPLUS' ENTERED AT 15:13:18 ON 28 SEP 2006
L7 3 SEA ABB=ON L5 AND L6 Inventor Search

Compd Search FILE 'REGISTRY' ENTERED AT 15:15:48 ON 28 SEP 2006
L8 1 SEA ABB=ON 309913-51-7/RN
L9 1 SEA ABB=ON 309913-51-7/RN Requested compd.

FILE 'HCAPLUS' ENTERED AT 15:16:44 ON 28 SEP 2006
L10 8 SEA ABB=ON L9
L11 1 SEA ABB=ON L10 AND ?DIABETES?
L12 8 SEA ABB=ON L10 OR L11
L13 6 SEA ABB=ON L12 AND (PRD<20031206 OR PD<20031206)

FILE 'MEDLINE, BIOSIS, EMBASE, JAPIO, JICST-EPLUS' ENTERED AT 15:17:49 ON 28 SEP 2006
L14 0 SEA ABB=ON L12

FILE 'USPATFULL' ENTERED AT 15:18:13 ON 28 SEP 2006
L15 5 SEA ABB=ON L12 AND (PRD<20031206 OR PD<20031206)

FILE 'HCAPLUS, USPATFULL' ENTERED AT 15:18:45 ON 28 SEP 2006
L16 9 DUP REMOV L13 L15 (2 DUPLICATES REMOVED) 9 cits for CA Plus & USPatFull

Text Search FILE 'REGISTRY' ENTERED AT 15:39:12 ON 28 SEP 2006
E P38 MAPK INHIBITOR/CN
L17 2 SEA ABB=ON ("P38 MAPK"/CN OR "P38 MAPK (BIOMPHALARIA GLABRATA STRAIN BS90 HEMOCYTE)"/CN OR "P38 MAPK INHIBITOR"/CN)

FILE 'HCAPLUS' ENTERED AT 15:39:42 ON 28 SEP 2006
L18 10002 SEA ABB=ON L17 OR P38(W)?MAPK?(W)?INHIBIT?

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L19          320 SEA ABB=ON  L18 AND ?DIABETES?
L20           25 SEA ABB=ON  L19 AND (TYPE(W)(1 OR I)(W)?DIABETES?)
L21            6 SEA ABB=ON  L20 AND (PRD<20021206 OR PD<20021206)

      FILE 'MEDLINE, BIOSIS, EMBASE, JAPIO, JICST-EPLUS' ENTERED AT 15:41:28 ON
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L22           23 SEA ABB=ON  L20

      FILE 'USPATFULL' ENTERED AT 15:42:04 ON 28 SEP 2006
L23           28 SEA ABB=ON  L20 AND (PRD<20021206 OR PD<20021206)

      FILE 'USPATFULL, HCAPLUS' ENTERED AT 15:43:04 ON 28 SEP 2006
L24           34 DUP REMOV L23 L21 (0 DUPLICATES REMOVED)

      FILE HOME

      FILE HCAPLUS

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      FILE COVERS 1907 - 28 Sep 2006  VOL 145 ISS 14
      FILE LAST UPDATED: 27 Sep 2006  (20060927/ED)

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      FILE REGISTRY
      Property values tagged with IC are from the ZIC/VINITI data file
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      STRUCTURE FILE UPDATES:   27 SEP 2006  HIGHEST RN 909000-49-3
      DICTIONARY FILE UPDATES:  27 SEP 2006  HIGHEST RN 909000-49-3

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      TSCA INFORMATION NOW CURRENT THROUGH June 30, 2006

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      http://www.cas.org/ONLINE/UG/regprops.html

      FILE MEDLINE
       FILE LAST UPDATED: 27 Sep 2006 (20060927/UP).  FILE COVERS 1950 TO DATE.
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23 cits from

34 cits from CAPlus + USPatFull

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 is now (26 Feb.) available. For details on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE BIOSIS
FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 27 September 2006 (20060927/ED)

FILE EMBASE
FILE COVERS 1974 TO 28 Sep 2006 (20060928/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

EMBASE is now updated daily. SDI frequency remains weekly (default) and biweekly.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE JAPIO
FILE LAST UPDATED: 3 APR 2006 <20060403/UP>
FILE COVERS APRIL 1973 TO DECEMBER 22, 2005

>>> GRAPHIC IMAGES AVAILABLE <<<

>>> NEW IPC8 DATA AND FUNCTIONALITY NOT YET AVAILABLE IN THIS FILE.
USE IPC7 FORMAT FOR SEARCHING THE IPC. WATCH THIS SPACE FOR FURTHER
DEVELOPMENTS AND SEE OUR NEWS SECTION FOR FURTHER INFORMATION
ABOUT THE IPC REFORM <<<

FILE JICST-EPLUS
FILE COVERS 1985 TO 26 SEP 2006 (20060926/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED TERM (/CT) THESAURUS RELOAD.

FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 28 Sep 2006 (20060928/PD)
FILE LAST UPDATED: 28 Sep 2006 (20060928/ED)
HIGHEST GRANTED PATENT NUMBER: US7114185
HIGHEST APPLICATION PUBLICATION NUMBER: US2006218687

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CA INDEXING IS CURRENT THROUGH 28 Sep 2006 (20060928/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 28 Sep 2006 (20060928/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2006


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SESSION RESUMED IN FILE 'MEDLINE, BIOSIS, EMBASE, JAPIO, JICST-EPLUS'
AT 15:52:54 ON 28 SEP 2006
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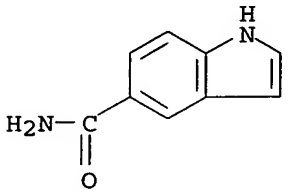
INVENTOR SEARCH

=> d ibib abs hitstr l7 1-3

L7 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:658530 HCAPLUS
DOCUMENT NUMBER: 145:262961
TITLE: Preventive and therapeutic potential of p38α-selective mitogen-activated protein kinase inhibitor in nonobese diabetic mice with type 1 **diabetes**
AUTHOR(S): **Medicherla, Satyanarayana; Protter, Andrew A.**; Ma, Jing Ying; Mangadu, Ruban; Almirez, Ramona; Koppelman, Bruce; Kerr, Irene; Navas, Tony A.; Movius, Fabiola; Reddy, Mamatha; Liu, Yu-Wang; Luedtke, Gregory; Perumattam, John; Mavunkel, Babu; Dugar, Sundeep; **Schreiner, George F.**
CORPORATE SOURCE: Scios Inc., Fremont, CA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2006), 318(1), 99-107
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mitogen-activated protein kinases (MAPKs) and heat shock proteins (HSPs) are ubiquitous proteins that function within T cells in both normal and stress-related pathophysiol. states, including type 1 **diabetes.** The nonobese diabetic (NOD) mouse spontaneously develops T cell-mediated autoimmune pancreatic beta cell destruction that is similar to type 1 **diabetes** in humans. Because p38 MAPKs have been shown to modulate T cell function, we studied the effects of a p38α MAPK-selective inhibitor, indole-5-carboxamide (SD-169), on the development and progression of type 1 **diabetes** in the NOD mouse. In preventive treatment studies, SD-169 significantly reduced p38 and HSP60 expression in T cells of the pancreatic beta islets. Following treatment, the incidence of **diabetes** as determined by blood glucose levels was significantly lower, and immunohistochem. of pancreatic beta islet tissue demonstrated significant reduction in CD5+ T cell infiltration in the SD-169 treatment group as compared with untreated NOD mice. In therapeutic studies using mildly and moderately hyperglycemic NOD mice, SD-169 treatment lowered blood glucose and improved glucose homeostasis. Furthermore, following cessation of SD-169 treatment, NOD mice showed significant arrest of **diabetes.** In conclusion, we report that this p38α-selective inhibitor prevents the development and progression of **diabetes** in NOD mice by inhibiting T cell infiltration and activation, thereby preserving beta cell mass via inhibition of the p38 MAPK signaling pathway. These results have bearing on current prophylactic and therapeutic protocols using p38α-selective inhibitors in the prediabetic period for children at high risk of type 1 **diabetes**, in the honeymoon period, and for adults with latent autoimmune **diabetes.**

IT **1670-87-7**, SD 169
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(SD 169; preventive and therapeutic potential of p38α-selective MAPK inhibitor SD-169 in nonobese diabetic mice with type 1 **diabetes**)
RN 1670-87-7 HCAPLUS
CN 1H-Indole-5-carboxamide (9CI) (CA INDEX NAME)



IT **165245-96-5**, p38 MAP kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (preventive and therapeutic potential of p38α-selective MAPK inhibitor SD-169 in nonobese diabetic mice with type 1 **diabetes**)
RN 165245-96-5 HCAPLUS
CN Kinase (phosphorylating), protein, RK (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:546407 HCAPLUS
DOCUMENT NUMBER: 141:82337
TITLE: Treatment of obesity and associated conditions with TGF-β inhibitors
INVENTOR(S): **Medicherla, Satyanarayana; Protter, Andrew A.; Schreiner, George F.**
PATENT ASSIGNEE(S): Scios, Inc., USA
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004056352	A1	20040708	WO 2003-US40907		20031218
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
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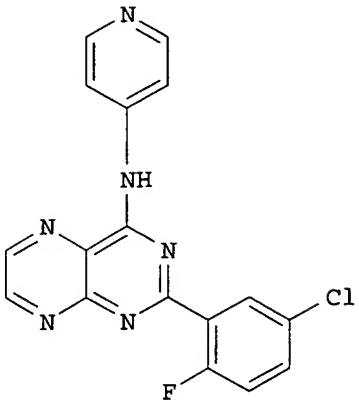
AU 2003297460	A1	20040714	AU 2003-297460		20031218
US 2004192583	A1	20040930	US 2003-742689		20031218
EP 1589960	A1	20051102	EP 2003-813828		20031218
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
JP 2006512369	T2	20060413	JP 2004-562359		20031218
PRIORITY APPLN. INFO.:			US 2002-435856P	P	20021219
			WO 2003-US40907	W	20031218

OTHER SOURCE(S): MARPAT 141:82337
GI



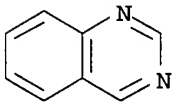
I

AB The invention concerns the treatment obesity and associated conditions with TGF-β inhibitors. More specifically, the invention concerns the use of TGF-β inhibitors in the treatment of obesity, type 2 **diabetes**, and pathol. conditions associated with obesity or type 2 **diabetes.** Quinazoline derivative I significantly restricted food intake and reduced the body weight of db/db obese mice. I also effectively modulated blood glucose levels.

IT **253-82-7D**, Quinazoline, derivs.
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as TGFβ inhibitor; TGF-β inhibitors for treatment of obesity and associated conditions)

RN 253-82-7 HCAPLUS

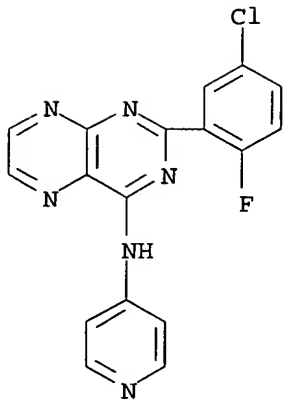
CN Quinazoline (6CI, 8CI, 9CI) (CA INDEX NAME)



IT **627536-09-8**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as TGFβ-R1 inhibitor; TGF-β inhibitors for treatment of obesity and associated conditions)

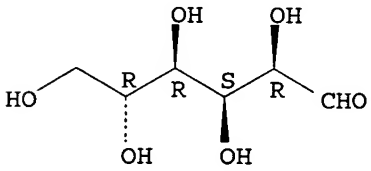
RN 627536-09-8 HCAPLUS

CN 4-Pteridinamine, 2-(5-chloro-2-fluorophenyl)-N-4-pyridinyl- (9CI) (CA INDEX NAME)



IT **50-99-7**, D-Glucose, biological studies
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(blood, treatment of damage caused to blood vessels, nerves and other internal structures by elevated levels of; TGF-β inhibitors for treatment of obesity and associated conditions)
RN 50-99-7 HCAPLUS
CN D-Glucose (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **152060-53-2**, Type I TGF-β receptor kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of signaling through; TGF-β inhibitors for treatment of obesity and associated conditions)
RN 152060-53-2 HCAPLUS
CN Kinase (phosphorylating), β-transforming growth factor type I receptor (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **9004-10-8**, Insulin, biological studies
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(resistance, treatment of; TGF-β inhibitors for treatment of obesity and associated conditions)
RN 9004-10-8 HCAPLUS
CN Insulin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:515679 HCAPLUS
DOCUMENT NUMBER: 141:47344

TITLE: Methods using p38 mitogen-activated protein kinase inhibitors for treating **diabetes**

INVENTOR(S): **Medicherla, Satyanarayana; Protter, Andrew A.; Schreiner, George F.**

PATENT ASSIGNEE(S): Scios Inc., USA

SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004053107	A2	20040624	WO 2003-US40140	20031205
WO 2004053107	A3	20041007		
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RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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AU 2003299652	A1	20040630	AU 2003-299652	20031205
US 2004171659	A1	20040902	US 2003-728665	20031205
EP 1583535	A2	20051012	EP 2003-799936	20031205
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006510654	T2	20060330	JP 2004-558236	20031205
PRIORITY APPLN. INFO.:			US 2002-431241P P	20021206
			WO 2003-US40140 W	20031205

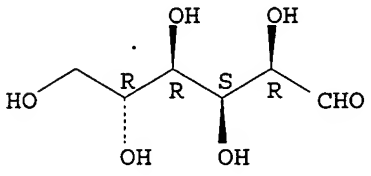
AB The invention discloses methods for treating **diabetes** by administering p38 mitogen-activated protein kinase inhibitors. The invention also discloses methods of decreasing blood glucose level in **diabetes** patients by administering p38 mitogen-activated protein kinase inhibitors.

IT **50-99-7**, D-Glucose, biological studies **9004-10-8**, Insulin, biological studies **165245-96-5**, p38 MAP kinase **176023-64-6**, p38γ MAP kinase **179800-23-8**, p38β Mitogen-activated protein kinase **192333-55-4**, p38δ MAP kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p38 MAP kinase inhibitors for treatment of **diabetes**)

RN 50-99-7 HCAPLUS

CN D-Glucose (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 9004-10-8 HCAPLUS
CN Insulin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 165245-96-5 HCAPLUS
CN Kinase (phosphorylating), protein, RK (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 176023-64-6 HCAPLUS
CN Kinase (phosphorylating), stress-activated protein, 3 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 179800-23-8 HCAPLUS
CN Kinase (phosphorylating), protein p38β (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 192333-55-4 HCAPLUS
CN Kinase (phosphorylating), protein, SAPK4 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
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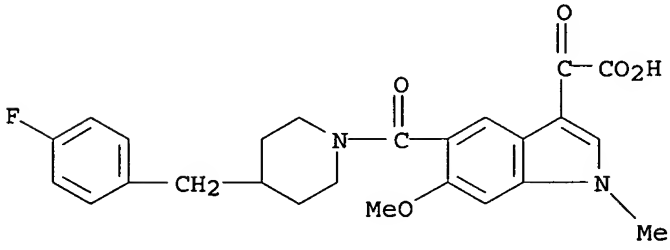
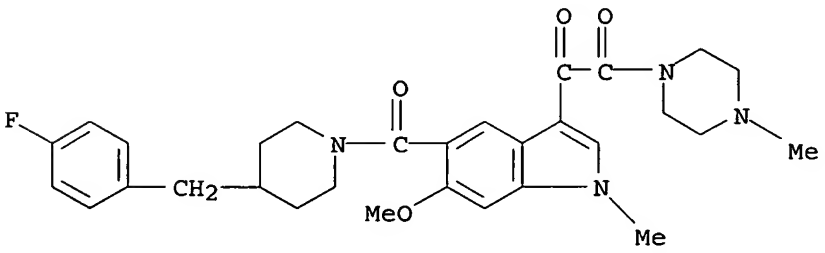
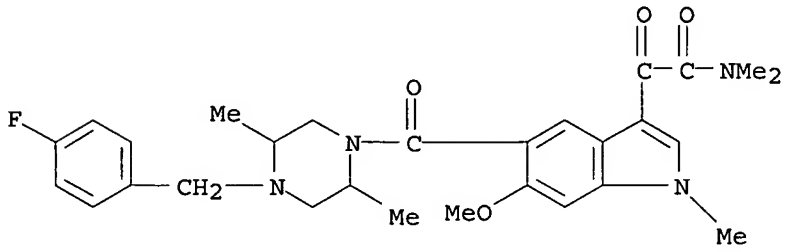
309914-09-8 309914-17-8 309914-25-8
309914-66-7 309914-79-2 309914-94-1
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(p38 MAP kinase inhibitors for treatment of **diabetes**)
RN 309913-28-8 HCAPLUS
CN 1H-Indole-3-acetic acid, 5-[[4-[(4-fluorophenyl)methyl]-1-piperidinyl]carbonyl]-6-methoxy-1-methyl-α-oxo- (9CI) (CA INDEX NAME)



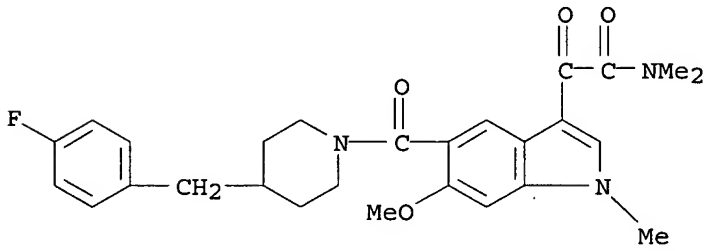
RN 309913-29-9 HCAPLUS
CN Piperazine, 1-[[5-[[4-[(4-fluorophenyl)methyl]-1-piperidinyl]carbonyl]-6-methoxy-1-methyl-1H-indol-3-yl]oxoacetyl]-4-methyl- (9CI) (CA INDEX NAME)



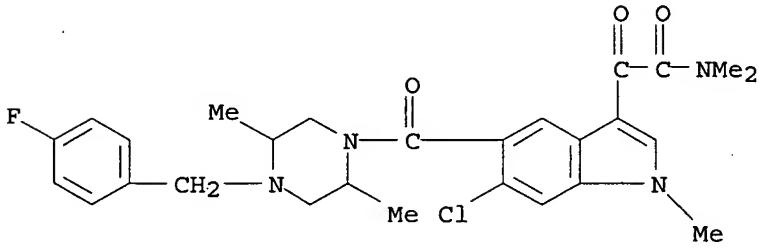
RN 309913-41-5 HCAPLUS
CN 1H-Indole-3-acetamide, 5-[[4-[(4-fluorophenyl)methyl]-2,5-dimethyl-1-piperazinyl]carbonyl]-6-methoxy-N,N,1-trimethyl-α-oxo- (9CI) (CA INDEX NAME)



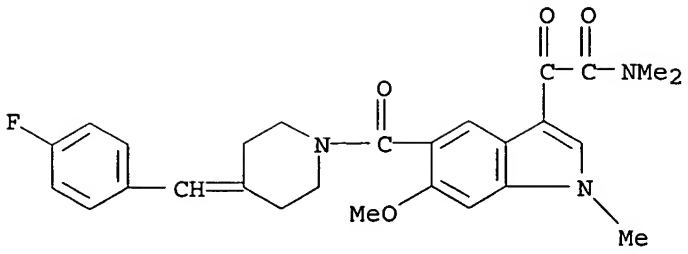
RN 309913-51-7 HCAPLUS
CN 1H-Indole-3-acetamide, 5-[[4-[(4-fluorophenyl)methyl]-1-piperidinyl]carbonyl]-6-methoxy-N,N,1-trimethyl-α-oxo- (9CI) (CA INDEX NAME)



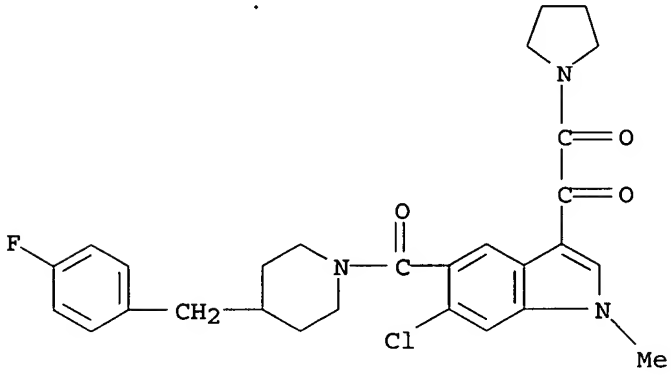
RN 309913-59-5 HCAPLUS
CN 1H-Indole-3-acetamide, 6-chloro-5-[[4-[(4-fluorophenyl)methyl]-2,5-dimethyl-1-piperazinyl]carbonyl]-N,N,1-trimethyl-α-oxo- (9CI) (CA INDEX NAME)



RN 309913-92-6 HCAPLUS
CN 1H-Indole-3-acetamide, 5-[[4-[(4-fluorophenyl)methylene]-1-piperidinyl]carbonyl]-6-methoxy-N,N,1-trimethyl-α-oxo- (9CI) (CA INDEX NAME)

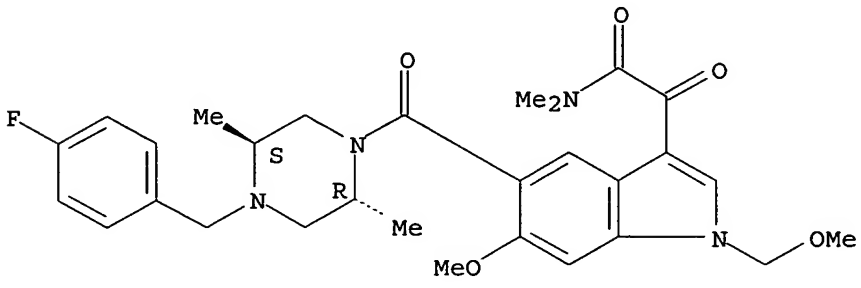


RN 309914-09-8 HCAPLUS
CN Piperidine, 1-[[6-chloro-1-methyl-3-(oxo-1-pyrrolidinylacetyl)-1H-indol-5-yl]carbonyl]-4-[(4-fluorophenyl)methyl]- (9CI) (CA INDEX NAME)



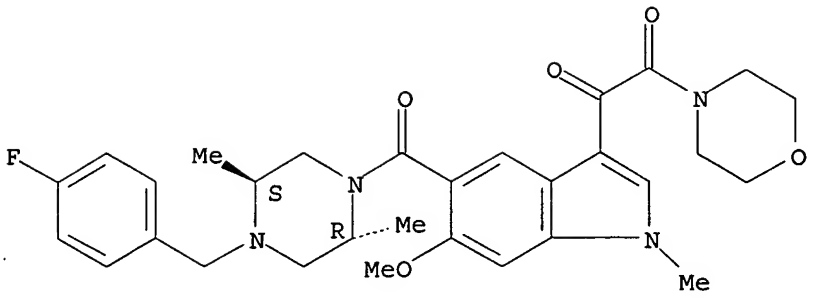
RN 309914-17-8 HCAPLUS
CN 1H-Indole-3-acetamide, 5-[[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethyl-1-piperazinyl]carbonyl]-6-methoxy-1-(methoxymethyl)-N,N-dimethyl-α-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

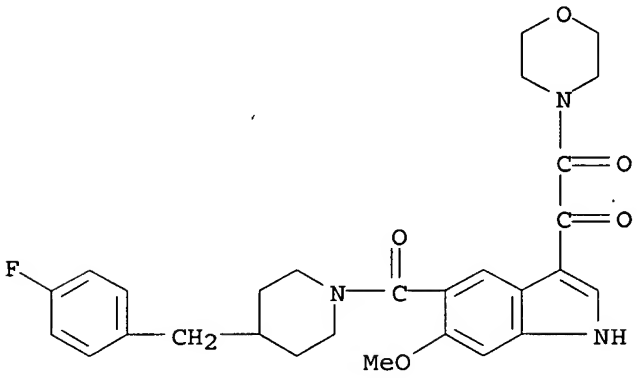


RN 309914-25-8 HCAPLUS
CN Morpholine, 4-[[5-[[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethyl-1-piperazinyl]carbonyl]-6-methoxy-1-methyl-1H-indol-3-yl]oxoacetyl]- (9CI) (CA INDEX NAME)

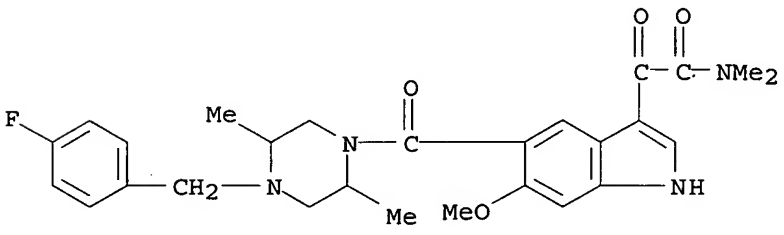
Absolute stereochemistry.



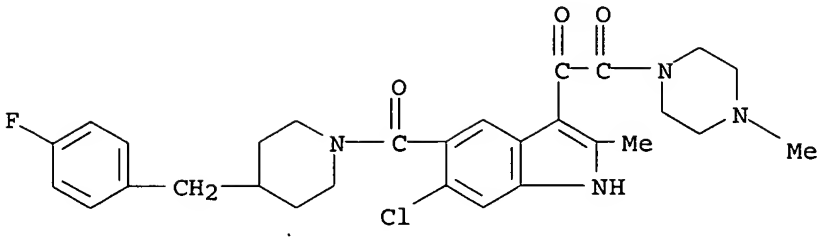
RN 309914-66-7 HCAPLUS
CN Morpholine, 4-[[5-[[4-[(4-fluorophenyl)methyl]-1-piperidinyl]carbonyl]-6-methoxy-1H-indol-3-yl]oxoacetyl]- (9CI) (CA INDEX NAME)



RN 309914-79-2 HCAPLUS
CN 1H-Indole-3-acetamide, 5-[[4-[(4-fluorophenyl)methyl]-2,5-dimethyl-1-piperazinyl]carbonyl]-6-methoxy-N,N-dimethyl-α-oxo- (9CI) (CA INDEX NAME)



RN 309914-94-1 HCAPLUS
CN Piperazine, 1-[[6-chloro-5-[[4-[(4-fluorophenyl)methyl]-1-piperidinyl]carbonyl]-2-methyl-1H-indol-3-yl]oxoacetyl]-4-methyl- (9CI) (CA INDEX NAME)



DISPLAY OF ELECTED SPECIE

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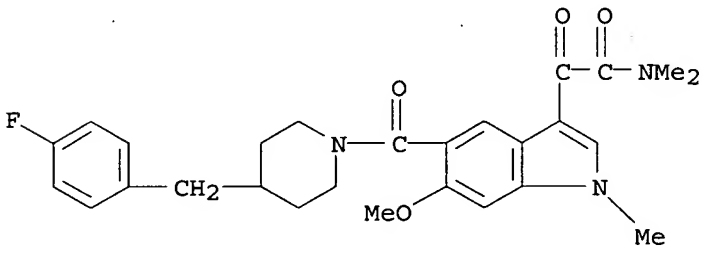
L8 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN
RN **309913-51-7** REGISTRY
ED Entered STN: 20 Dec 2000
CN 1H-Indole-3-acetamide, 5-[[4-[(4-fluorophenyl)methyl]-1-piperidinyl]carbonyl]-6-methoxy-N,N,1-trimethyl-α-oxo- (9CI) (CA INDEX NAME)
MF C27 H30 F N3 O4
SR CA
LC STN Files: CA, CAPLUS, PROUSDDR, SYNTHLINE, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

8 REFERENCES IN FILE CA (1907 TO DATE)
8 REFERENCES IN FILE CAPLUS (1907 TO DATE)
ED Entered STN: 20 Dec 2000

COMPOUND SEARCH - CAPLUS & USPATFULL SEARCH

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L9             1 SEA FILE=REGISTRY ABB=ON  309913-51-7/RN
L10            8 SEA FILE=HCAPLUS ABB=ON  L9
L11            1 SEA FILE=HCAPLUS ABB=ON  L10 AND ?DIABETES?
L12            8 SEA FILE=HCAPLUS ABB=ON  L10 OR L11
L13            6 SEA FILE=HCAPLUS ABB=ON  L12 AND (PRD<20031206 OR PD<20031206)
L15            5 SEA FILE=USPATFULL ABB=ON  L12 AND (PRD<20031206 OR PD<20031206
                 )
L16            9 DUP REMOV L13 L15 (2 DUPLICATES REMOVED)

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L16  ANSWER 1 OF 9  HCAPLUS  COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2005:162022  HCAPLUS
DOCUMENT NUMBER:          142:254591
TITLE:                    Methods of screening for compounds that selectively
                          inhibit p38 MAP kinase α isoenzymes for use as
                          immunomodulators
INVENTOR(S):              Kirschenbaum, Ford; Higgins, Linda S.; Schreiner,
                          George F.
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 41 pp., Cont.-in-part of U.S.
                          Ser. No. 683,656.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   3
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     ---------------      ----   --------    --------------------     --------
     US 2005043212         A1    20050224    US 2004-830834           20040422 <--
     US 2004176598         A1    20040909    US 2003-683656           20031009 <--
PRIORITY APPLN. INFO.:                       US 2002-417599P      P   20021009 <--
                                             US 2003-683656       A2  20031009 <--
AB   The invention relates to methods of screening for compds. that selectively
     inhibit p38 MAP kinase α isoenzymes for use as immunomodulators.
     Inhibitors of p38 MAP kinase α isoenzyme include siRNA and SB203580.
IT   309913-51-7
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (methods of screening for compds. that selectively inhibit p38 MAP
        kinase α isoenzymes for use as immunomodulators)
RN   309913-51-7  HCAPLUS
CN   1H-Indole-3-acetamide, 5-[[4-[(4-fluorophenyl)methyl]-1-
     piperidinyl]carbonyl]-6-methoxy-N,N,1-trimethyl-α-oxo- (9CI)  (CA
     INDEX NAME)
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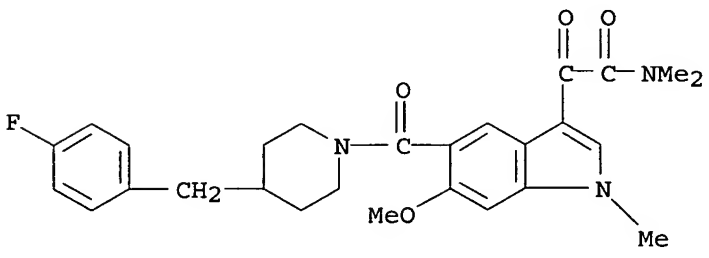
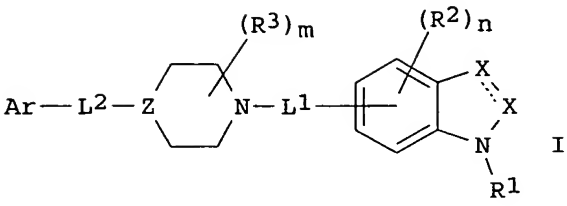


L16 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2005:232421 HCAPLUS
DOCUMENT NUMBER: 142:316692
TITLE: Preparation of indolylcarboxamide derivatives as inhibitors of p38 kinase
INVENTOR(S): Mavunkel, Babu J.; Chakravarty, Sarvajit; Perumattam, John J.; Dugar, Sundeep; Lu, Qing; Liang, Xi
PATENT ASSIGNEE(S): Scios, Inc., USA
SOURCE: U.S., 65 pp., Cont.-in-part of U.S. 6,589,954.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
US 6867209	B1	20050315	US 2000-575060		20000519	<--
US 6130235	A	20001010	US 1998-128137		19980803	<--
US 6340685	B1	20020122	US 1999-275176		19990324	<--
US 6589954	B1	20030708	US 1999-316761		19990521	<--
US 2003158417	A1	20030821	US 2002-146703		20020514	<--
US 2003144520	A1	20030731	US 2002-157048		20020528	<--
US 6864260	B2	20050308				
US 2003162970	A1	20030828	US 2002-156996		20020528	<--
US 2003195355	A1	20031016	US 2002-156997		20020528	<--
PRIORITY APPLN. INFO.:			US 1998-86531P	P	19980522	<--
			US 1998-128137	A2	19980803	<--
			US 1999-275176	A2	19990324	<--
			US 1999-316761	A2	19990521	<--
			US 1999-154594P	P	19990917	<--
			US 2000-202608P	P	20000509	<--
			US 2000-575060	A1	20000519	<--

OTHER SOURCE(S): MARPAT 142:316692
GI



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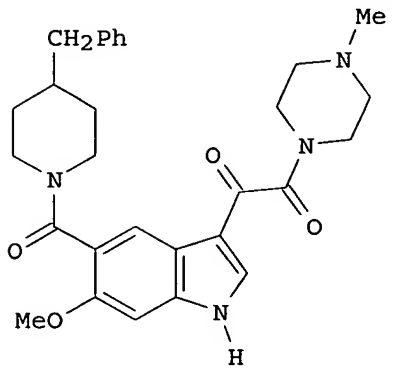


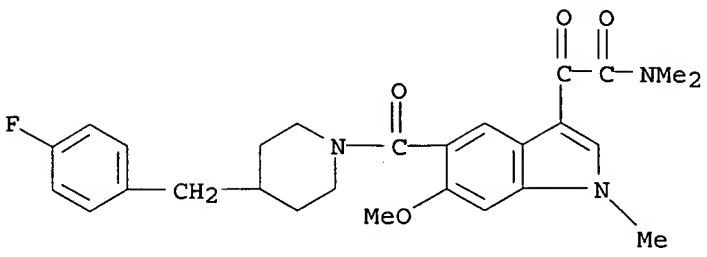
II

AB Title compds. I [X independently = CA, CR4A, CR5, CR52, NR6, or N; L1 = CO, SO2, or alkylene; L2 = (un)substituted-alkylene or -alkenylene; Ar = (un)substituted aryl group with substituents consisting of alkyl, alkenyl, halo, CN, etc.; Z = N or CR7 wherein R7 = H or non-interfering substituent; R1 = H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, etc.; R2 independently = halo, alkyl, OH, alkoxy, etc.; R3 independently = CN, CF3, NO2, alkyl, aryl, acyl, etc.; R4 = H, halo, alkyl or alkenyl; R5 independently = H, halo, alkyl, OH, etc.; R6 = H, alkyl, alkenyl, aryl, acyl, aroyl, etc.; A = -WiCOXjY wherein Y is COR8 wherein R8 = H, (un)substituted-alkyl, -alkenyl, -alkynyl, etc.; W and X = (un)substituted-alkylene, -alkenylene, -alkynylene; Y = tetrazole, 1,2,3-triazole, 1,2,4-triazole, or imidazole and each of i and j independently = 0 or 1; m = 0-4; n = 0-3], and their pharmaceutically acceptable salts are prepared and disclosed as useful for treatment of rheumatoid arthritis. Thus, e.g., II, was prepared by carbonylation of 6-methoxy-(4-benzylpiperidinyl)-indole-5-carboxamide with oxalyl chloride and subsequent amination using 4-methylpiperazine. ELISA assays for evaluation of inhibition of p38 kinase by I revealed that all compds. of the invention possessed IC50 values in the range of 0.1-1.5 μM. I as inhibitors of p38 kinase should prove useful in the treatment of rheumatoid arthritis.

IT **309913-51-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of indolylcarboxamide derivs. as p38 kinase inhibitors)

RN 309913-51-7 HCAPLUS

CN 1H-Indole-3-acetamide, 5-[[4-[(4-fluorophenyl)methyl]-1-piperidinyl]carbonyl]-6-methoxy-N,N,1-trimethyl-α-oxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:515679 HCAPLUS
DOCUMENT NUMBER: 141:47344
TITLE: Methods using p38 mitogen-activated protein kinase inhibitors for treating **diabetes**
INVENTOR(S): Medicherla, Satyanarayana; Protter, Andrew A.; Schreiner, George F.
PATENT ASSIGNEE(S): Scios Inc., USA
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004053107	A2	20040624	WO 2003-US40140	20031205 <--
WO 2004053107	A3	20041007		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2511763	AA	20040624	CA 2003-2511763	20031205 <--
AU 2003299652	A1	20040630	AU 2003-299652	20031205 <--
US 2004171659	A1	20040902	US 2003-728665	20031205 <--
EP 1583535	A2	20051012	EP 2003-799936	20031205 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006510654	T2	20060330	JP 2004-558236	20031205 <--
PRIORITY APPLN. INFO.:			US 2002-431241P P	20021206 <--
			WO 2003-US40140 W	20031205 <--

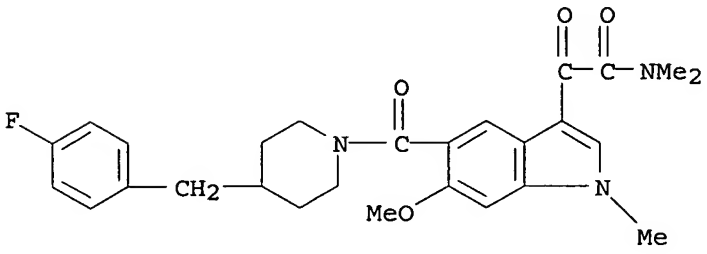
AB The invention discloses methods for treating **diabetes** by administering p38 mitogen-activated protein kinase inhibitors. The invention also discloses methods of decreasing blood glucose level in **diabetes** patients by administering p38 mitogen-activated protein kinase inhibitors.

IT **309913-51-7**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(p38 MAP kinase inhibitors for treatment of **diabetes**)

RN 309913-51-7 HCAPLUS

CN 1H-Indole-3-acetamide, 5-[[4-[(4-fluorophenyl)methyl]-1-piperidinyl]carbonyl]-6-methoxy-N,N,1-trimethyl-α-oxo- (9CI) (CA INDEX NAME)



L16 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:203623 HCAPLUS

DOCUMENT NUMBER: 140:247108

TITLE: Bone healing and promoting osteogenesis by administration of a p38 MAP kinase inhibitor

INVENTOR(S): Protter, Andrew Asher; Liu, David Y.

PATENT ASSIGNEE(S): Scios Inc., USA

SOURCE: PCT Int. Appl., 127 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004019873	A2	20040311	WO 2003-US26839	20030829 <--
WO 2004019873	C2	20040624		
WO 2004019873	A3	20041007		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2497240	AA	20040311	CA 2003-2497240	20030829 <--
AU 2003262911	A1	20040319	AU 2003-262911	20030829 <--
US 2004162289	A1	20040819	US 2003-651934	20030829 <--
EP 1539121	A2	20050615	EP 2003-791848	20030829 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006508051	T2	20060309	JP 2004-531559	20030829 <--
PRIORITY APPLN. INFO.:			US 2002-406664P P	20020829 <--
			WO 2003-US26839 W	20030829 <--

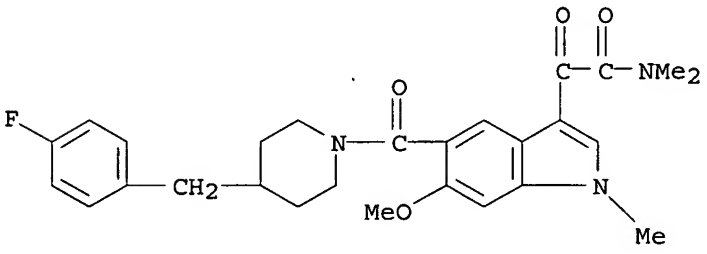
OTHER SOURCE(S): MARPAT 140:247108

AB The invention discloses methods of bone healing by administering a p38 MAP kinase inhibitor. Specifically, the invention provides methods of

treating bone fractures, bone diseases, bone grafting, especially enhancing bone
healing following facial reconstruction, maxillary reconstruction, mandibular reconstruction or tooth extraction, enhancing long bone extension, enhancing prosthetic ingrowth, and increasing bone synostosis by administering a p38 MAP kinase inhibitor.

IT **309913-51-7**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bone healing and promoting osteogenesis by administration of a p38 MAP kinase inhibitor)

RN 309913-51-7 HCAPLUS
CN 1H-Indole-3-acetamide, 5-[[4-[(4-fluorophenyl)methyl]-1-piperidinyl]carbonyl]-6-methoxy-N,N,1-trimethyl-α-oxo- (9CI) (CA INDEX NAME)



L16 ANSWER 5 OF 9 USPATFULL on STN

ACCESSION NUMBER:	2004:221887 USPATFULL		
TITLE:	Methods for treating **diabetes**		
INVENTOR(S):	Medicherla, Satyanarayana, Cupertino, CA, UNITED STATES Protter, Andrew A., Palo Alto, CA, UNITED STATES Schreiner, George F., Los Altos, CA, UNITED STATES		

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004171659	A1	20040902
APPLICATION INFO.:	US 2003-728665	A1	20031205 (10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2002-431241P	20021206 (60)	<--

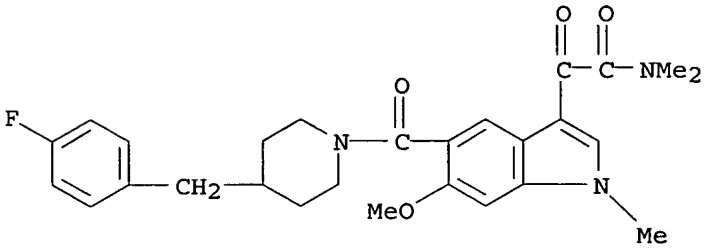
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	MORRISON & FOERSTER LLP, 3811 VALLEY CENTRE DRIVE, SUITE 500, SAN DIEGO, CA, 92130-2332
NUMBER OF CLAIMS:	11
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	10 Drawing Page(s)
LINE COUNT:	3428

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention is directed to methods of treating **diabetes** by administering p38 mitogen activated protein kinase inhibitors. The invention is also directed to methods of decreasing blood glucose level in **diabetes** patients by administering p38 mitogen activated protein kinase inhibitors.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **309913-51-7**
(p38 MAP kinase inhibitors for treatment of diabetes)
RN 309913-51-7 USPATFULL
CN 1H-Indole-3-acetamide, 5-[[4-[(4-fluorophenyl)methyl]-1-piperidinyl]carbonyl]-6-methoxy-N,N,1-trimethyl-α-oxo- (9CI) (CA INDEX NAME)



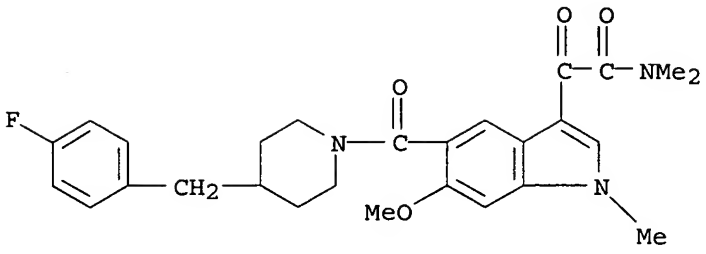
L16 ANSWER 6 OF 9 USPATFULL on STN
ACCESSION NUMBER: 2004:209855 USPATFULL
TITLE: Methods of promoting osteogenesis
INVENTOR(S): Protter, Andrew A., Palo Alto, CA, UNITED STATES
Liu, David Y., Palo Alto, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004162289	A1	20040819
APPLICATION INFO.:	US 2003-651934	A1	20030829 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-406664P	20020829 (60) <--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MORRISON & FOERSTER LLP, 3811 VALLEY CENTRE DRIVE, SUITE 500, SAN DIEGO, CA, 92130-2332
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 13 Drawing Page(s)
LINE COUNT: 3708
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention is directed to methods of bone healing by administering a p38 MAP kinase inhibitor. The invention is directed to methods of treating bone fractures, bone diseases, bone grafting, especially enhancing bone healing following facial reconstruction, maxillary reconstruction, mandibular reconstruction or tooth extraction, enhancing long bone extension, enhancing prosthetic ingrowth, and increasing bone synostosis by administering a p38 MAP kinase inhibitor.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **309913-51-7**
(bone healing and promoting osteogenesis by administration of a p38 MAP kinase inhibitor)
RN 309913-51-7 USPATFULL
CN 1H-Indole-3-acetamide, 5-[[4-[(4-fluorophenyl)methyl]-1-piperidinyl]carbonyl]-6-methoxy-N,N,1-trimethyl-α-oxo- (9CI) (CA INDEX NAME)



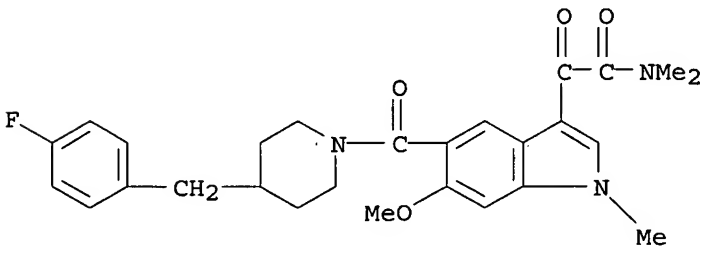
L16 ANSWER 7 OF 9 USPATFULL on STN
ACCESSION NUMBER: 2004:13467 USPATFULL
TITLE: Method to treat cystic fibrosis
INVENTOR(S): Higgins, Linda S., Palo Alto, CA, UNITED STATES
Liu, David Y., Palo Alto, CA, UNITED STATES
Protter, Andrew A., Palo Alto, CA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004009990	A1	20040115	
APPLICATION INFO.:	US 2002-291243	A1	20021108	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2001-338209P	20011109 (60)	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Kate H. Murashige, Morrison & Foerster LLP, Suite 500, 3811 Valley Centre Drive, San Diego, CA, 92130
NUMBER OF CLAIMS: 40
EXEMPLARY CLAIM: 1
LINE COUNT: 1187
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention is directed to methods to treat cystic fibrosis by administering certain imidazole derivatives.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **309913-51-7P**
(imidazole derivs. for treatment of cystic fibrosis)
RN 309913-51-7 USPATFULL
CN 1H-Indole-3-acetamide, 5-[[4-[(4-fluorophenyl)methyl]-1-piperidinyl]carbonyl]-6-methoxy-N,N,1-trimethyl-α-oxo- (9CI) (CA INDEX NAME)



L16 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:396662 HCAPLUS
DOCUMENT NUMBER: 138:379271
TITLE: Method using imidazole derivatives to treat cystic fibrosis
INVENTOR(S): Higgins, Linda S.; Liu, David Y.; Protter, Andrew A.
PATENT ASSIGNEE(S): Scios Inc., USA
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003041644	A2	20030522	WO 2002-US35939	20021108 <--
WO 2003041644	A3	20031113		
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2466665	AA	20030522	CA 2002-2466665	20021108 <--
US 2004009990	A1	20040115	US 2002-291243	20021108 <--
EP 1453515	A2	20040908	EP 2002-778799	20021108 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002014020	A	20041013	BR 2002-14020	20021108 <--
TR 200401028	T2	20041122	TR 2004-1028	20021108 <--
JP 2005511616	T2	20050428	JP 2003-543531	20021108 <--

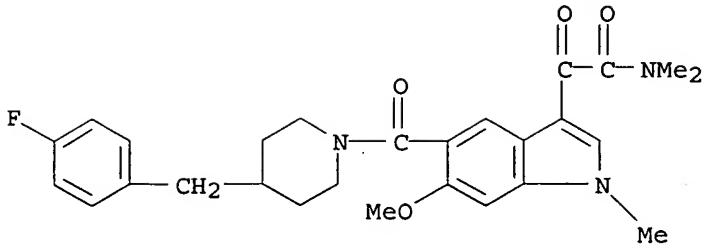
PRIORITY APPLN. INFO.: US 2001-338209P P 20011109 <--
WO 2002-US35939 W 20021108 <--

OTHER SOURCE(S): MARPAT 138:379271

AB The invention is directed to methods to treat cystic fibrosis by administering certain imidazole derivs.

IT **309913-51-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(imidazole derivs. for treatment of cystic fibrosis)

RN 309913-51-7 HCAPLUS
CN 1H-Indole-3-acetamide, 5-[[4-[(4-fluorophenyl)methyl]-1-piperidinyl]carbonyl]-6-methoxy-N,N,1-trimethyl-α-oxo- (9CI) (CA INDEX NAME)



L16 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:842127 HCAPLUS
DOCUMENT NUMBER: 134:17503
TITLE: Preparation of 5-[4-benzylpiperidinyl(piperazinyl)]-indolecarboxamides as inhibitors of p38 kinase
INVENTOR(S): Mavunkel, Babu J.; Chakravarty, Sarvajit; Perumattam, John J.; Dugar, Sundeep; Lu, Qing; Liang, Xi
PATENT ASSIGNEE(S): Scios Inc., USA
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

US Pat 6,864,260

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
WO 2000071535	A1	20001130	WO 2000-US14003		20000519	<--
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG						
US 6589954	B1	20030708	US 1999-316761		19990521	<--
CA 2372567	AA	20001130	CA 2000-2372567		20000519	<--
EP 1178983	A1	20020213	EP 2000-939322		20000519	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO						
BR 2000011274	A	20020226	BR 2000-11274		20000519	<--
NZ 515285	A	20040130	NZ 2000-515285		20000519	<--
AU 772295	B2	20040422	AU 2000-54424		20000519	<--
RU 2278115	C2	20060620	RU 2001-134501		20000519	<--
BG 106091	A	20020628	BG 2001-106091		20011108	<--
HR 2001000854	A1	20030430	HR 2001-854		20011119	<--
NO 2001005655	A	20020118	NO 2001-5655		20011120	<--
AU 2004203356	A1	20040819	AU 2004-203356		20040722	<--
PRIORITY APPLN. INFO.:			US 1999-316761	A	19990521	<--
			US 1999-154594P	P	19990917	<--
			US 2000-202608P	P	20000509	<--
			US 1998-86531P	P	19980522	<--
			US 1998-128137	A2	19980803	<--
			US 1999-275176	A2	19990324	<--
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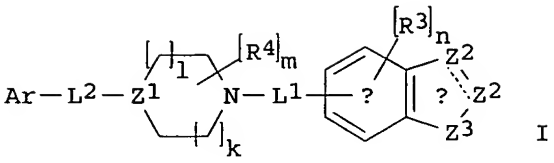
OTHER SOURCE(S): MARPAT 134:17503

GI



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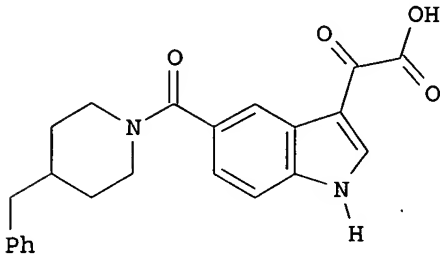


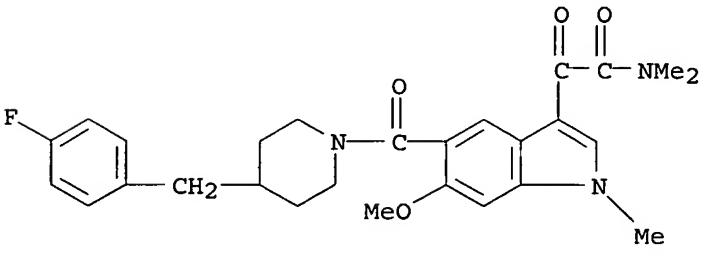
II

AB The title compds. [I; one Z2 = CA, CR8A and the other = CR1, CR12, NR6, N (wherein R1, R6, R8 = H, noninterfering substituent; A = WiCOXjY; Y = COR2, an isostere; R2 = H, noninterfering substituent; W, X = spacer of 2-6Å; i, j = 0-1); Z3 = NR7, O; R3 = noninterfering substituent; n = 0-3; L1, L2 = linker; R4 = noninterfering substituent; m = 0-4; Z1 = CR5, N (R5 = H, noninterfering substituent); l, k = 0-2, wherein the sum of l and k = 0-3; Ar = aryl substituted with 0-5 noninterfering substituents, wherein two noninterfering substituents can form a fused ring; the distance between the atom of Ar linked to L2 and the center of the α ring is 4.5-24Å] which inhibit p38-α kinase (biol. data given), were prepared Thus, treating 6-methoxy-(4-benzylpiperidinyl)-indole-5-carboxamide with oxalyl chloride in CH2Cl2 afforded the indole-5-carboxamide II.

IT **309913-51-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 5-[4-benzylpiperidinyl(piperazinyl)]-indolecarboxamides as inhibitors of p38 kinase)

RN 309913-51-7 HCAPLUS

CN 1H-Indole-3-acetamide, 5-[[4-[(4-fluorophenyl)methyl]-1-piperidinyl]carbonyl]-6-methoxy-N,N,1-trimethyl-α-oxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TEXT SEARCH - CAPLUS & USPATFULL

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=> d que stat l24
L17           2 SEA FILE=REGISTRY ABB=ON  ("P38 MAPK"/CN OR "P38 MAPK (BIOMPHAL
                ARIA GLABRATA STRAIN BS90 HEMOCYTE)"/CN OR "P38 MAPK INHIBITOR"
                /CN)
L18       10002 SEA FILE=HCAPLUS ABB=ON  L17 OR P38(W)?MAPK?(W)?INHIBIT?
L19         320 SEA FILE=HCAPLUS ABB=ON  L18 AND ?DIABETES?
L20          25 SEA FILE=HCAPLUS ABB=ON  L19 AND (TYPE(W)(1 OR I)(W)?DIABETES?)
L21           6 SEA FILE=HCAPLUS ABB=ON  L20 AND (PRD<20021206 OR PD<20021206)
L23          28 SEA FILE=USPATFULL ABB=ON  L20 AND (PRD<20021206 OR PD<20021206
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L24          34 DUP REMOV L23 L21 (0 DUPLICATES REMOVED)

=> d ibib abs l24 1-34

L24  ANSWER 1 OF 34  USPATFULL on STN
ACCESSION NUMBER:        2006:175374  USPATFULL
TITLE:                   Protein kinase inhibitors
INVENTOR(S):             Burns, Christopher John, Melbourne, AUSTRALIA
                         Bu, Xianyong, Rosanna East, AUSTRALIA
                         Wilks, Andrew Frederick, South Yarra, AUSTRALIA

                              NUMBER        KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 2006148824      A1   20060706
APPLICATION INFO.:       US 2006-367248     A1   20060302  (11)
RELATED APPLN. INFO.:    Continuation of Ser. No. US 2003-469303, filed on 29
                         Aug 2003, PENDING A 371 of International Ser. No. WO
                         2003-AU629, filed on 23 May 2003

                                NUMBER         DATE
                         ------------------ --------
PRIORITY INFORMATION:    AU 2002-20020000251520020523                <--
                         US 2002-399070P    20020726 (60)            <--
DOCUMENT TYPE:           Utility
FILE SEGMENT:            APPLICATION
LEGAL REPRESENTATIVE:    MORRISON & FOERSTER LLP, 12531 HIGH BLUFF DRIVE, SUITE
                         100, SAN DIEGO, CA, 92130-2040, US
NUMBER OF CLAIMS:        24
EXEMPLARY CLAIM:         1
NUMBER OF DRAWINGS:      2 Drawing Page(s)
LINE COUNT:              1671
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     A compound of the general formula:    ##STR1##  or pharmaceutically
       acceptable salts, hydrates, solvates, crystal forms of diastereomers
       thereof is described. Method of inhibiting a protein kinase using
       compounds of Formula I are also described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24  ANSWER 2 OF 34  USPATFULL on STN
ACCESSION NUMBER:        2006:22076  USPATFULL
TITLE:                   Methods for treating and preventing insulin resistance
                         and related disorders
INVENTOR(S):             Greenberg, Andrew S., Boston, MA, UNITED STATES
```

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2006019910	A1	20060126
APPLICATION INFO.:	US 2004-977328	A1	20041029 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-690647, filed on 17 Oct 2000, GRANTED, Pat. No. US 6897019
Continuation-in-part of Ser. No. WO 1999-US8364, filed on 16 Apr 1999, PENDING

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1998-82152P	19980417 (60)	<--
	US 1998-82741P	19980423 (60)	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FOLEY HOAG, LLP, PATENT GROUP, WORLD TRADE CENTER WEST, 155 SEAPORT BLVD, BOSTON, MA, 02110, US
NUMBER OF CLAIMS: 37
EXEMPLARY CLAIM: 1-18
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 2759
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides methods, therapeutics and kits for treating and preventing diseases or conditions associated with excessive lipolysis, in particular TNF-α induced lipolysis, and/or excessive free fatty acid levels. Exemplary conditions include insulin-resistance, **diabetes**, in particular NIDDM, obesity, glucose intolerance, hyperinsulinemia, polycystic ovary syndrome, and coronary artery disease. In a preferred embodiment, the method includes administering to a subject in need a pharmaceutically effective amount of an inhibitor of the JNK signal transduction pathway and/or an inhibitor of the MAPK/ERK signal transduction pathway.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 3 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2006:169991 USPATFULL
TITLE: Substituted pyrazoles as p38 kinase inhibitors
INVENTOR(S): Naraian, Ashok S., Ballwin, MO, UNITED STATES
Clare, Michael, Skokie, IL, UNITED STATES
Collins, Paul W., Deerfield, IL, UNITED STATES
Crich, Joyce Zuowu, Glenview, IL, UNITED STATES
Devraj, Rajesh, Ballwin, MO, UNITED STATES
Flynn, Daniel L., Natick, MA, UNITED STATES
Geng, Lifeng, Skokie, IL, UNITED STATES
Graneto, Matthew J., Chesterfield, MO, UNITED STATES
Hanau, Cathleen E., Chesterfield, MO, UNITED STATES
Hanson, Gunnar J., Skokie, IL, UNITED STATES
Hartmann, Susan J., Kirkwood, MO, UNITED STATES
Hepperle, Michael, Boston, MA, UNITED STATES
Huang, He, Chicago, IL, UNITED STATES
Khanna, Ish K., Libertyville, IL, UNITED STATES
Koszyk, Francis J., Prospect Heights, IL, UNITED STATES
Liao, Shuyuan, Northbrook, IL, UNITED STATES
Metz, Suzanne, Chesterfield, MO, UNITED STATES
Naing, Win, Chesterfield, MO, UNITED STATES
Partis, Richard A., Evanston, IL, UNITED STATES
Perry, Thao D., Chesterfield, MO, UNITED STATES
Rao, Shashidhar N., St. Louis, MO, UNITED STATES

Selness, Shaun Raj, Chesterfield, MO, UNITED STATES
South, Michael S., St. Louis, MO, UNITED STATES
Stealey, Michael A., Libertyville, IL, UNITED STATES
Talley, John Jeffrey, Cambridge, MA, UNITED STATES
Vazquez, Michael L., Ballwin, MO, UNITED STATES
Walker, John, Maryland Heights, MO, UNITED STATES
Weier, Richard M., Lake Bluff, IL, UNITED STATES
Xu, Xiangdong, Gurnee, IL, UNITED STATES
Yang, Syaulan, Chesterfield, MO, UNITED STATES
Yu, Yi, Glenville, IL, UNITED STATES

PATENT ASSIGNEE(S): Pharmacia Corporation, St. Louis, MO, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 7071198	B1	20060704
APPLICATION INFO.:	US 2004-840734		20040505 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2001-21780, filed on 7 Dec 2001, PENDING Division of Ser. No. US 2000-513351, filed on 24 Feb 2000, Pat. No. US 6525059 Continuation-in-part of Ser. No. US 1998-196623, filed on 20 Nov 1998, Pat. No. US 6514977

mentioned diabetes

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-47570P	19970522 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Solola, Taofiq
LEGAL REPRESENTATIVE: Lappin, Julie M.
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 18479
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A class of pyrazole derivatives is described for use in treating p38 kinase mediated disorders. Compounds of particular interest are defined by Formula IA ##STR1## wherein R.sup.1, R.sup.2, R.sup.3 and R.sup.4 are as described in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 4 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2005:197195 USPATFULL
TITLE: Mammalian tribbles signaling pathways and methods and reagents related thereto
INVENTOR(S): Dower, Steven, Sheffield, UNITED KINGDOM
Quanstrom, Eva, Sheffield, UNITED KINGDOM
Kiss-Toth, Endre, Sheffield, UNITED KINGDOM

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005171338	A1	20050804
APPLICATION INFO.:	US 2003-466020	A1	20020108 (10)
	WO 2002-US70		20020108

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-260294P	20010108 (60)

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DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MINTZ, LEVIN, COHN, FERRIS, GLOVSKY, AND POPEO, P.C., ONE FINANCIAL CENTER, BOSTON, MA, 02111, US
NUMBER OF CLAIMS: 41
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Page(s)
LINE COUNT: 5751
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides methods and reagents for modulating mitogen activated protein kinase pathways using mammalian tribbles homologs (htrb).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 5 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2005:171875 USPATFULL
TITLE: Jnk inhibitor
INVENTOR(S): Itoh, Fumio, Ibaraki, JAPAN
Kimura, Hiroyuki, Osaka, JAPAN
Igata, Hideki, Osaka, JAPAN
Kawamoto, Tomohiro, Osaka, JAPAN
Sasaki, Mitsuru, Osaka, JAPAN
Kitamura, Shuji, Osaka, JAPAN

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2005148624	A1	20050707	
APPLICATION INFO.:	US 2003-504132	A1	20030212	(10)
	WO 2003-JP1429		20030212	

	NUMBER	DATE
PRIORITY INFORMATION:	JP 2002-35073	20020213
	JP 2003-2002251997	20020829

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TAKEDA PHARMACEUTICALS NORTH AMERICA, INC, INTELLECTUAL PROPERTY DEPARTMENT, 475 HALF DAY ROAD, SUITE 500, LINCOLNSHIRE, IL, 60069, US
NUMBER OF CLAIMS: 72
EXEMPLARY CLAIM: 1
LINE COUNT: 11597
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A JNK inhibitor containing a compound having an isoquinolinone skeleton or a salt thereof, such as a compound represented by the formula ##STR1## wherein ring A and ring B are each an optionally substituted benzene ring, X is --O--, --N.dbd., --NR.sup.3-- or --CHR.sup.3--, R.sup.2 is an acyl group, an optionally esterified or thioesterified carboxyl group, an optionally substituted carbamoyl group or an optionally substituted amino group and the like, a broken line shows a single bond or a double bond, and R.sup.1 is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group and the like, and the like.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 6 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2005:171787 USPATFULL
TITLE: Methods for treating and preventing insulin resistance and related disorders

INVENTOR(S): Greenberg, Andrew S., Boston, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005148536	A1	20050707
APPLICATION INFO.:	US 2004-977116	A1	20041029 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-690647, filed on 17 Oct 2000, PENDING Continuation-in-part of Ser. No. WO 1999-US8364, filed on 16 Apr 1999, PENDING

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1998-82152P	19980417 (60)	<--
	US 1998-82741P	19980423 (60)	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FOLEY HOAG, LLP, PATENT GROUP, WORLD TRADE CENTER WEST, 155 SEAPORT BLVD, BOSTON, MA, 02110, US
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 2690
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides methods, therapeutics and kits for treating and preventing diseases or conditions associated with excessive lipolysis, in particular TNF-α induced lipolysis, and/or excessive free fatty acid levels. Exemplary conditions include insulin-resistance, **diabetes**, in particular NIDDM, obesity, glucose intolerance, hyperinsulinemia, polycystic ovary syndrome, and coronary artery disease. In a preferred embodiment, the method includes administering to a subject in need a pharmaceutically effective amount of an inhibitor of the JNK signal transduction pathway and/or an inhibitor of the MAPK/ERK signal transduction pathway.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 7 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2005:43617 USPATFULL
TITLE: Nucleic acid array
INVENTOR(S): Stuhlmuller, Bruno, Berlin, GERMANY, FEDERAL REPUBLIC OF
Haupl, Thomas, Erkner, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S): PathoArray GmbH, Berlin, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005037344	A1	20050217
APPLICATION INFO.:	US 2002-278698	A1	20021023 (10)

	NUMBER	DATE	
PRIORITY INFORMATION:	DE 2001-10155600	20011109	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WELSH & KATZ, LTD, 120 S RIVERSIDE PLAZA, 22ND FLOOR, CHICAGO, IL, 60606
NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
LINE COUNT: 2642

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB It is proposed to use selectioned monocyte macrophage genes to provide tools for diagnostic, prognostic and therapy-monitoring analysis and for performing screenings for pharmacologically active substances and substance classes of chronic inflammatory diseases, chronic inflammatory diseases induced by bacteria, arteriosclerosis, tumors, organ and tissue transplantations, and sepsis when examining blood, tissue, purified or cultivated cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 8 OF 34 USPATFULL on STN

ACCESSION NUMBER: 2005:126974 USPATFULL
TITLE: Methods for treating and preventing insulin resistance and related disorders
INVENTOR(S): Greenberg, Andrew S., 711 Washington St., Boston, MA, UNITED STATES 02111

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6897019	B1	20050524
APPLICATION INFO.:	US 2000-690647		20001017 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 1999-US8364, filed on 16 Apr 1999, PENDING

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1998-82741P	19980423 (60)	<--
	US 1998-82152P	19980417 (60)	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: LeGuyader, John L.
ASSISTANT EXAMINER: Schultz, J D
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 26 Drawing Figure(s); 14 Drawing Page(s)
LINE COUNT: 2976

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides methods, therapeutics and kits for treating and preventing diseases or conditions associated with excessive lipolysis, in particular TNF-α induced lipolysis, and/or excessive free fatty acid levels. Exemplary conditions include insulin-resistance, **diabetes**, in particular NIDDM, obesity, glucose intolerance, hyperinsulinemia, polycystic ovary syndrome, and coronary artery disease. In a preferred embodiment, the method includes administering to a subject in need a pharmaceutically effective amount of an inhibitor of the JNK signal transduction pathway and/or an inhibitor of the MAPK/ERK signal transduction pathway.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 9 OF 34 USPATFULL on STN

ACCESSION NUMBER: 2004:334786 USPATFULL
TITLE: Method for the detection of depression related gene transcripts in blood
INVENTOR(S): Liew, Choong-Chin, Toronto, CANADA
PATENT ASSIGNEE(S): ChondroGene Limited (non-U.S. corporation)

	NUMBER	KIND	DATE

PATENT INFORMATION: US 2004265868 A1 20041230
APPLICATION INFO.: US 2004-812702 A1 20040330 (10)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2004-802875, filed on 12 Mar 2004, PENDING Continuation-in-part of Ser. No. US 2003-601518, filed on 20 Jun 2003, PENDING Continuation-in-part of Ser. No. US 2002-268730, filed on 9 Oct 2002, PENDING Continuation of Ser. No. US 2000-477148, filed on 4 Jan 2000, ABANDONED

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1999-115125P	19990106 (60)	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PALMER & DODGE, LLP, KATHLEEN M. WILLIAMS, 111 HUNTINGTON AVENUE, BOSTON, MA, 02199
NUMBER OF CLAIMS: 48
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 34 Drawing Page(s)
LINE COUNT: 5805
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed to detection and measurement of gene transcripts and their equivalent nucleic acid products in blood. Specifically provided is analysis performed on a drop of blood for detecting, diagnosing and monitoring diseases using gene-specific and/or tissue-specific primers. The present invention also describes methods by which delineation of the sequence and/or quantitation of the expression levels of disease-specific genes allows for an immediate and accurate diagnostic/prognostic test for disease or to assess the effect of a particular treatment regimen.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 10 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2004:299993 USPATFULL
TITLE: Protein kinase inhibitors
INVENTOR(S): Burns, Christopher John, Seddon, AUSTRALIA
Bu, Xianyong, Rosanna East, AUSTRALIA
Wilks, Andrew Frederick, South Yarra, AUSTRALIA

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004235862	A1	20041125	
APPLICATION INFO.:	US 2003-469303	A1	20031204	(10)
	WO 2003-AU629		20030523	

	NUMBER	DATE	
PRIORITY INFORMATION:	AU 2002-2515	20020523	<--
	US 2002-399070P	20020726 (60)	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MORRISON & FOERSTER LLP, 3811 VALLEY CENTRE DRIVE, SUITE 500, SAN DIEGO, CA, 92130-2332
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: CLM-01-24
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 1645
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A compound of the general formula: ##STR1##

or pharmaceutically acceptable salts, hydrates, solvates, crystal forms of diastereomers thereof is described. A method of treating protein kinase-associated disease states using the compound of Formula I is also described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 11 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2004:228047 USPATFULL
TITLE: Substituted pyrazoles as p38 kinase inhibitors
INVENTOR(S): Naraian, Ashok S., Ballwin, MO, UNITED STATES
Clare, Michael, Skokie, IL, UNITED STATES
Collins, Paul W., Deerfield, IL, UNITED STATES
Crich, Joyce Zuowu, Glenview, IL, UNITED STATES
Devraj, Rajesh, Ballwin, MO, UNITED STATES
Flynn, Daniel L., Natick, MA, UNITED STATES
Geng, Lifeng, Skokie, IL, UNITED STATES
Graneto, Matthew J., Chesterfield, MO, UNITED STATES
Hanau, Cathleen E., Chesterfield, MO, UNITED STATES
Hanson, Gunnar J., Skokie, IL, UNITED STATES
Hartmann, Susan J., Kirkwood, MO, UNITED STATES
Hepperle, Michael, Boston, MA, UNITED STATES
Huang, He, Northbrook, IL, UNITED STATES
Koszyk, Francis J., Prospect Heights, IL, UNITED STATES
Liao, Shuyuan, Northbrook, IL, UNITED STATES
Metz, Suzanne, Chesterfield, MO, UNITED STATES
Partis, Richard A., Evanston, IL, UNITED STATES
Perry, Thao D., Chesterfield, MO, UNITED STATES
Rao, Shashidhar N., St. Louis, MO, UNITED STATES
Selness, Shaun Raj, Chesterfield, MO, UNITED STATES
South, Michael S., St. Louis, MO, UNITED STATES
Stealey, Michael A., Libertyville, IL, UNITED STATES
Talley, John Jeffrey, Cambridge, MA, UNITED STATES
Vazquez, Michael L., Ballwin, MO, UNITED STATES
Weier, Richard M., Lake Bluff, IL, UNITED STATES
Xu, Xiangdong, Gurnee, IL, UNITED STATES
Khanna, Ish K., Libertyville, IL, UNITED STATES
Yu, Yi, Glenview, IL, UNITED STATES
Naing, Win, Chesterfield, MO, UNITED STATES
Yang, Syaulan, Chesterfield, MO, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004176433	A1	20040909
APPLICATION INFO.:	US 2003-374781	A1	20030225 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2002-114297, filed on 2 Apr 2002, GRANTED, Pat. No. US 6617324 Division of Ser. No. US 2001-918481, filed on 31 Jul 2001, GRANTED, Pat. No. US 6423713 Division of Ser. No. US 1998-196623, filed on 20 Nov 1998, GRANTED, Pat. No. US 6514977 Continuation-in-part of Ser. No. US 1998-83670, filed on 22 May 1998, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-47570P	19970522 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: David M. Gryte, Harness, Dickey & Pierce, P.L.C., Suite

400, 7700 Bonhomme, St. Louis, MO, 63105
NUMBER OF CLAIMS: 184
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 21540
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A class of pyrazole derivatives is described for use in treating p38 kinase mediated disorders. Compounds of particular interest are defined by Formula IA ##STR1##

wherein R.sup.1, R.sup.2, R.sup.3 and R.sup.4 are as described in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 12 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2004:204017 USPATFULL
TITLE: 4-Aryl substituted indolinones
INVENTOR(S): Cui, Jingrong, Foster City, CA, UNITED STATES
Zhang, Ruofei, Foster City, CA, UNITED STATES
Shen, Hong, San Francisco, CA, UNITED STATES
Chu, Ji Yu, Fremont, CA, UNITED STATES
Zhang, Fang-Jie, San Jose, CA, UNITED STATES
Koenig, Marcel, Burlingame, CA, UNITED STATES
Do, Steven Huy, San Jose, CA, UNITED STATES
Li, Xiaoyuan, Los Altos, CA, UNITED STATES
Wei, Chung Chen, Foster City, CA, UNITED STATES
Tang, Peng Cho, Moraga, CA, UNITED STATES
PATENT ASSIGNEE(S): Sugen, Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004157909	A1	20040812
	US 6861418	B2	20050301
APPLICATION INFO.:	US 2003-736243	A1	20031216 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2001-23488, filed on 20 Dec 2001, GRANTED, Pat. No. US 6677368

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-256479P	20001220 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FOLEY AND LARDNER, SUITE 500, 3000 K STREET NW, WASHINGTON, DC, 20007
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
LINE COUNT: 13339
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to 4-arylindolinones, as well as pharmaceutical compositions thereof, capable of modulating protein kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation. The present invention also relates to methods for treating protein kinase related disorders.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 13 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2004:77185 USPATFULL
TITLE: Substituted pyridinones

INVENTOR(S): Devadas, Balekudru, Chesterfield, MO, UNITED STATES
Walker, John, Maryland Heights, MO, UNITED STATES
Selness, Shaun R., Chesterfield, MO, UNITED STATES
Boehm, Terri L., Ballwin, MO, UNITED STATES
Durley, Richard C., Chesterfield, MO, UNITED STATES
Devraj, Rajesh, Ballwin, MO, UNITED STATES
Hickory, Brian S., Wildwood, MO, UNITED STATES
Rucker, Paul V., University City, MO, UNITED STATES
Jerome, Kevin D., Maryland Heights, MO, UNITED STATES
Madsen, Heather M., University City, MO, UNITED STATES
Alvira, Edgardo, Chesterfield, MO, UNITED STATES
Promo, Michele A., Maryland Heights, MO, UNITED STATES
Blevis-Bal, Radhika M., St. Louis, MO, UNITED STATES
Marruto, Laura D., Ellisville, MO, UNITED STATES
Hitchcock, Jeff, Saint Peters, MO, UNITED STATES
Owen, Thomas, Chesterfield, MO, UNITED STATES
Naing, Win, Chesterfield, MO, UNITED STATES
Xing, Li, Chesterfield, MO, UNITED STATES
Shieh, Huey S., St. Louis, MO, UNITED STATES
Sambandam, Aruna, Guilderland, NY, UNITED STATES
Liu, Shuang, Schenectady, NY, UNITED STATES
Scott, Ian L., Woodinville, WA, UNITED STATES
McGee, Kevin F., Guilderland, NY, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004058964	A1	20040325	
	US 7067540	B2	20060627	
APPLICATION INFO.:	US 2003-367987	A1	20030214	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-357029P	20020214 (60)
	US 2002-436915P	20021230 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Steven J. Sarussi, McDonnell Boehnen Hulbert & Berghoff, 32nd Floor, 300 S. Wacker Drive, Chicago, IL, 60606
NUMBER OF CLAIMS: 76
EXEMPLARY CLAIM: 1
LINE COUNT: 26020
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are compounds Formula I ##STR1##

and pharmaceutically acceptable salts thereof, wherein R.sub.1, R.sub.2, R.sub.3, R.sub.4, and R.sub.5 are defined herein. These compounds are useful for treating diseases and conditions caused or exacerbated by unregulated p38 MAP Kinase and/or TNF activity. Pharmaceutical compositions containing the compounds, methods of preparing the compounds and methods of treatment using the compounds are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 14 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2003:300912 USPATFULL
TITLE: Combinations of peroxisome proliferator-activated receptor-alpha agonists and cyclooxygenase-2 selective inhibitors and therapeutic uses therefor

INVENTOR(S): Obukowicz, Mark G., Kirkwood, MO, UNITED STATES
PATENT ASSIGNEE(S): Pharmacia Corporation, St. Louis, MO, UNITED STATES, 63141 (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003212138	A1	20031113	
APPLICATION INFO.:	US 2003-341217	A1	20030113	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2002-348297P	20020114 (60)	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Charles E. Dunlap, Keenan Building, Third Floor, 1330 Lady Street, Columbia, SC, 29201
NUMBER OF CLAIMS: 59
EXEMPLARY CLAIM: 1
LINE COUNT: 4257
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods for the treatment, prevention, or inhibition of pain, inflammation, or inflammation-related disorder, and for the treatment or inhibition of cardiovascular disease or disorder, and for the treatment or inhibition of cancer, and for the treatment of Alzheimer's disease in a subject in need of such treatment, prevention, or inhibition, include treating the subject with a peroxisome proliferator activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or prodrug thereof. Compositions, pharmaceutical compositions and kits for effecting the particular methods are also described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 15 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2003:225250 USPATFULL
TITLE: Combinations of a cyclooxygenase-2 selective inhibitor and a TNFalpha antagonist and therapeutic uses therefor
INVENTOR(S): Bennett, Dennis A., Wildwood, MO, UNITED STATES
PATENT ASSIGNEE(S): Pharmacia Corporation, St. Louis, MO, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003157061	A1	20030821	
APPLICATION INFO.:	US 2002-310454	A1	20021205	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2001-337802P	20011205 (60)	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Charles E. Dunlap, Keenan Building, Third Floor, 1330 Lady Street, Columbia, SC, 29201
NUMBER OF CLAIMS: 75
EXEMPLARY CLAIM: 1
LINE COUNT: 3289
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for the prevention, treatment, or inhibition of pain, inflammation, or inflammation-related disorder and for the prevention, treatment, or inhibition of a cardiovascular disease or disorder in a subject that is in need of such prevention, treatment or inhibition,

involves the administration to the subject of a cyclooxygenase-2 selective inhibitor or prodrug thereof and a TNFα antagonist. A method can also involve the treatment, prevention, or inhibition of cancer in a subject in need of such treatment, prevention, or inhibition, by administering to the subject a cyclooxygenase-2 selective inhibitor or prodrug thereof and a TNFα antagonist which is selected from the group consisting of a compound that affects the synthesis of TNFα, a compound that inhibits the binding of TNFα with a receptor specific for TNFα, and a compound that interferes with intracellular signaling triggered by TNFα binding with a receptor. Compositions, pharmaceutical compositions and kits that can be used with the methods are also described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 16 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2003:187403 USPATFULL
TITLE: Tumor necrosis factor-gamma
INVENTOR(S): Yu, Guo-Liang, Berkeley, CA, UNITED STATES
Ni, Jian, Germantown, MD, UNITED STATES
Rosen, Craig A., Laytonsville, MD, UNITED STATES
Zhang, Jun, San Diego, CA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003129189	A1	20030710	
APPLICATION INFO.:	US 2002-226294	A1	20020823	(10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-899059, filed on 6 Jul 2001, PENDING Continuation-in-part of Ser. No. US 2000-559290, filed on 27 Apr 2000, ABANDONED Continuation-in-part of Ser. No. US 1999-246129, filed on 8 Feb 1999, PENDING Continuation-in-part of Ser. No. US 1998-131237, filed on 7 Aug 1998, PENDING Continuation-in-part of Ser. No. US 1998-5020, filed on 9 Jan 1998, ABANDONED Continuation-in-part of Ser. No. US 1995-461246, filed on 5 Jun 1995, ABANDONED Continuation-in-part of Ser. No. WO 1994-US12880, filed on 7 Nov 1994, PENDING

	NUMBER	DATE		
PRIORITY INFORMATION:	US 2001-314381P	20010824	(60)	<--
	US 2001-278449P	20010326	(60)	<--
	US 2000-216879P	20000707	(60)	<--
	US 2000-180908P	20000208	(60)	<--
	US 1999-134067P	19990513	(60)	<--
	US 1999-132227P	19990503	(60)	<--
	US 1999-131963P	19990430	(60)	<--
	US 1998-74047P	19980209	(60)	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 49
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 33 Drawing Page(s)
LINE COUNT: 13325
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Human TNF-gamma-alpha and TNF-gamma-beta polypeptides and DNA (RNA) encoding such polypeptides and a procedure for producing such

polypeptides by recombinant techniques are disclosed. Also disclosed are methods for utilizing such polypeptides to inhibit cellular growth, for example in a tumor or cancer, for facilitating wound-healing, to provide resistance against infection, induce inflammatory activities, and stimulating the growth of certain cell types to treat diseases, for example restenosis. Also disclosed are diagnostic methods for detecting a mutation in the TNF-gamma-alpha and TNF-gamma-beta nucleic acid sequences or overexpression of the TNF-gamma-alpha and/or TNF-gamma-beta polypeptides. Antagonists against such polypeptides and their use as a therapeutic to treat cachexia, septic shock, cerebral malaria, inflammation, arthritis and graft-rejection are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 17 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2003:100186 USPATFULL
TITLE: 4-aryl substituted indolinones
INVENTOR(S): Cui, Jingrong Jean, Foster City, CA, UNITED STATES
Zhang, Ruofei, Foster City, CA, UNITED STATES
Shen, Hong, San Francisco, CA, UNITED STATES
Chu, Ji Yu, Fremont, CA, UNITED STATES
Zhang, Fang-Jie, San Jose, CA, UNITED STATES
Koenig, Marcel, Burlingame, CA, UNITED STATES
Do, Steven Huy, San Jose, CA, UNITED STATES
Li, Xiaoyuan, Los Altos, CA, UNITED STATES
Wei, Chung Chen, Foster City, CA, UNITED STATES
Tang, Peng Cho, Moraga, CA, UNITED STATES
PATENT ASSIGNEE(S): Sugen, Inc. (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003069297	A1	20030410	
	US 6677368	B2	20040113	
APPLICATION INFO.:	US 2001-23488	A1	20011220	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-256479P	20001220 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FOLEY AND LARDNER, SUITE 500, 3000 K STREET NW, WASHINGTON, DC, 20007
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 14189
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to 4-arylindolinones, as well as pharmaceutical compositions thereof, capable of modulating protein kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation. The present invention also relates to methods for treating protein kinase related disorders.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 18 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2003:79103 USPATFULL
TITLE: Use of carboxy compounds such as 2(4-acetoxyphenyl)-2-chloro-N-methyl-ethylammonium chloride as anti-inflammatory agents
INVENTOR(S): De Bosscher, Karolien, Zottegem, BELGIUM

Berghe, Wim Vanden, Gentbrugge, BELGIUM
Haegeman, Guy, Balegem, BELGIUM

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003055030	A1	20030320
	US 7053120	B2	20060530
APPLICATION INFO.:	US 2002-177987	A1	20020621 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 2000-EP13347, filed on 21 Dec 2000, UNKNOWN

	NUMBER	DATE	
PRIORITY INFORMATION:	EP 1999-204433	19991221	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TRASKBRITT, PC, P.O. Box 2550, Salt Lake City, UT, 84110
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 1147
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the use of specific carboxy compounds, more specifically to the use of 2(4-acetoxyphenyl)-2-chloro-N-methyl-ethylammonium chloride, in the treatment of inflammatory diseases. Part of the invention is also a composition, preferably a pharmaceutical composition, comprising as active ingredient at least 2 (4-acetoxyphenyl)-2-chloro-N-methyl-ethylammonium chloride together with (pharmaceutically) acceptable excipients.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 19 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2003:57074 USPATFULL
TITLE: Carbon monoxide improves outcomes in tissue and organ transplants and suppresses apoptosis
INVENTOR(S): Bach, Fritz H., Manchester-by-the-Sea, MA, UNITED STATES
Otterbein, Leo E., New Kensington, PA, UNITED STATES
Soares, Miguel P., Boston, MA, UNITED STATES
Tobiasch, Edda M., Bonn, GERMANY, FEDERAL REPUBLIC OF
Gose, Jeanne, Manchester-by-the-Sea, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003039638	A1	20030227
APPLICATION INFO.:	US 2002-177930	A1	20020621 (10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2001-300289P	20010621 (60)	<--
	US 2001-334340P	20011129 (60)	<--
	US 2001-337974P	20011207 (60)	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FISH & RICHARDSON PC, 225 FRANKLIN ST, BOSTON, MA, 02110
NUMBER OF CLAIMS: 149
EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 31 Drawing Page(s)
LINE COUNT: 3473
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention features methods for transplanting organs, tissues and individual cells. Also featured are methods for maintaining cells in vitro and for enhancing survival and/or function of cells following transplantation. The methods include the administration of carbon monoxide in an amount sufficient to enhance cell survival and/or function.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 20 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2003:51146 USPATFULL
TITLE: Methods and compositions for diagnosis and treatment of vascular conditions
INVENTOR(S): Pillarisetti, Sivaram, Norcross, GA, UNITED STATES
Wang, Dongyan, Norcross, GA, UNITED STATES
Saxena, Uday, Atlanta, GA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003036103	A1	20030220	
APPLICATION INFO.:	US 2002-210896	A1	20020731	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2001-309012P	20010731 (60)	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: JOHN S. PRATT, ESQ, KILPATRICK STOCKTON, LLP, 1100 PEACHTREE STREET, SUITE 2800, ATLANTA, GA, 30309
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 1032
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed to methods and compositions for the diagnosis and treatment of vascular conditions, particularly **diabetes** and atherosclerosis. The present invention comprises methods and compositions for determining the expression or activity of enzymes effecting HSPG, preferably, heparanase. The invention also comprises methods and compositions for treatment of vasculophathic diseases comprising administration of therapeutic compounds that are effective in inhibiting the expression or activity of heparanase.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 21 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2003:37639 USPATFULL
TITLE: TUMOR NECROSIS FACTOR-GAMMA
INVENTOR(S): YU, GUO-LIANG, SAN MATEO, CA, UNITED STATES
NI, JIAN, ROCKVILLE, MD, UNITED STATES
ROSEN, CRAIG A., LAYTONSVILLE, MD, UNITED STATES
ZHANG, JUN, BETHESDA, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003027284	A1	20030206
	US 6599719	B2	20030729

APPLICATION INFO.: US 1998-131237 A1 19980807 (9)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-5020, filed on 9 Jan 1998, ABANDONED Continuation-in-part of Ser. No. US 1995-461246, filed on 5 Jun 1995, ABANDONED Continuation-in-part of Ser. No. WO 1994-US12880, filed on 7 Nov 1994, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-74047P	19980209 (60) <--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 41
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Page(s)
LINE COUNT: 6325
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Human TNF-gamma-alpha and TNF-gamma-beta polypeptides and DNA (RNA) encoding such polypeptides and a procedure for producing such polypeptides by recombinant techniques is disclosed. Also disclosed are methods for utilizing such polypeptides to inhibit cellular growth, for example in a tumor or cancer, for facilitating wound-healing, to provide resistance against infection, induce inflammatory acitvities, and stimulating the growth of certain cell types to treat diseases, for example restenosis. Also disclosed are diagnostic methods for detecting a mutation in the TNF-gamma-alpha and TNF-gamma-beta nucleic acid sequences or overexperession of the TNF-gamma-alpha and TNF-gamma-beta polypeptides. Antagonists against such polypeptides and their use as a therapeutic to treat cachexia, septic shock, cerebral malaria, inflammation, arthritis and graft-rejection are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 22 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2003:240399 USPATFULL
TITLE: Substituted pyrazoles as p38 kinase inhibitors
INVENTOR(S): Naraian, Ashok S., Hainesville, IL, United States
Clare, Michael, Skokie, IL, United States
Collins, Paul W., Deerfield, IL, United States
Crich, Joyce Zuowu, Glenview, IL, United States
Devraj, Rajesh, Ballwin, MO, United States
Flynn, Daniel L., Clarkson Valley, MO, United States
Geng, Lifeng, Skokie, IL, United States
Graneto, Matthew J., Chesterfield, MO, United States
Hanau, Cathleen E., Chesterfield, MO, United States
Hanson, Gunnar J., Skokie, IL, United States
Hartmann, Susan J., Kirkwood, MO, United States
Hepperle, Michael, St. Charles, MO, United States
Huang, He, Chicago, IL, United States
Koszyk, Francis J., Prospect Heights, IL, United States
Liao, Shuyuan, Glen Ellyn, IL, United States
Metz, Suzanne, Chesterfield, MO, United States
Partis, Richard A., Evanston, IL, United States
Perry, Thao D., Chesterfield, MO, United States
Rao, Shashidhar N., St. Louis, MO, United States
Selness, Shaun Raj, Chesterfield, MO, United States
South, Michael S., St. Louis, MO, United States
Stealey, Michael A., Libertyville, IL, United States

Talley, John Jeffrey, St. Louis, MO, United States
Vazquez, Michael L., Ballwin, MO, United States
Weier, Richard M., Lake Bluff, IL, United States
Xi, Xiangdong, Evanston, IL, United States
Khanna, Ish K., Libertyville, IL, United States
Yu, Yi, Skokie, IL, United States

PATENT ASSIGNEE(S): G. D. Searle & Company, Skokie, IL, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6617324	B1	20030909
APPLICATION INFO.:	US 2002-114297		20020402 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2001-918481, filed on 31 Jul 2001, now patented, Pat. No. US 6423713 Division of Ser. No. US 1998-196623, filed on 20 Nov 1998 Continuation-in-part of Ser. No. US 1998-83670, filed on 22 May 1998, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-47570P	19970522 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Solola, T. A.
LEGAL REPRESENTATIVE: Gryte, David M., Harness, Dickey & Pierce, P.L.C.
NUMBER OF CLAIMS: 112
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 17190
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A class of pyrazole derivatives described for use in treating p38 kinase mediated disorders. Compounds of particular interest are defined by Formula IA ##STR1##

wherein R.sup.1, R.sup.2, R.sup.3 and R.sup.4 are as described in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 23 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2003:33482 USPATFULL
TITLE: Substituted pyrazoles as p38 kinase inhibitors
INVENTOR(S): Anantanarayan, Ashok, Hainesville, IL, United States
Clare, Michael, Skokie, IL, United States
Collins, Paul W., Deerfield, IL, United States
Crich, Joyce Zuowu, Glenview, IL, United States
Devraj, Rajesh, Ballwin, MO, United States
Flynn, Daniel L., Clarkson Valley, MO, United States
Geng, Lifeng, Skokie, IL, United States
Graneto, Matthew J., Chesterfield, MO, United States
Hanau, Cathleen E., Chesterfield, MO, United States
Hanson, Gunnar J., Skokie, IL, United States
Hartmann, Susan J., Kirkwood, MO, United States
Hepperle, Michael, St. Charles, MO, United States
Huang, He, Chicago, IL, United States
Koszyk, Francis J., Prospect Heights, IL, United States
Liao, Shuyuan, Glen Ellyn, IL, United States
Metz, Suzanne, Chesterfield, MO, United States
Partis, Richard A., Evanston, IL, United States

Perry, Thao D., Chesterfield, MO, United States
Rao, Shashidhar N., St. Louis, MO, United States
Selness, Shaun Raj, Chesterfield, MO, United States
South, Michael S., St. Louis, MO, United States
Stealey, Michael A., Libertyville, IL, United States
Talley, John Jeffrey, St. Louis, MO, United States
Vazquez, Michael L., Ballwin, MO, United States
Weier, Richard M., Lake Bluff, IL, United States
Xu, Xiangdong, Evanston, IL, United States
Khanna, Ish K., Libertyville, IL, United States
Yu, Yi, Skokie, IL, United States

PATENT ASSIGNEE(S): G.D. Searle & Company, Skokie, IL, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6514977	B1	20030204
APPLICATION INFO.:	US 1998-196623		19981120 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-83670, filed on 22 May 1998

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-47570P	19970522 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Solola, Taofiq A.
LEGAL REPRESENTATIVE: Williams, Scott A.
NUMBER OF CLAIMS: 92
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 16885
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A class of pyrazole derivatives is described for use in treating p38 kinase mediated disorders. Compounds of particular interest are defined by Formula IA ##STR1##

wherein R.sup.1, R.sup.2, R.sup.3 and R.sup.4 are as described in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 24 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2002:272419 USPATFULL
TITLE: Tumor necrosis factor-gamma
INVENTOR(S): Yu, Guo-Liang, Berkeley, CA, UNITED STATES
Ni, Jian, Germantown, MD, UNITED STATES
Rosen, Craig A., Laytonsville, MD, UNITED STATES
Zhang, Jun, Bethesda, MD, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002150534	A1	20021017	<--
APPLICATION INFO.:	US 2001-899059	A1	20010706 (9)	

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 2000-US11689, filed on 28 Apr 2000, UNKNOWN Continuation-in-part of Ser. No. US 1999-246129, filed on 8 Feb 1999, PENDING Continuation-in-part of Ser. No. US 1998-131237, filed on 7 Aug 1998, PENDING Continuation-in-part of Ser. No. US 1998-5020, filed on 9 Jan 1998, ABANDONED

Continuation-in-part of Ser. No. US 1995-461246, filed on 5 Jun 1995, ABANDONED Continuation-in-part of Ser. No. WO 1994-US12880, filed on 7 Nov 1994, UNKNOWN

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2001-278449P	20010326 (60)	<--
	US 2000-216879P	20000707 (60)	<--
	US 2000-180908P	20000208 (60)	<--
	US 1999-134067P	19990513 (60)	<--
	US 1999-132227P	19990503 (60)	<--
	US 1999-131963P	19990430 (60)	<--
	US 1998-74047P	19980209 (60)	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 49
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 33 Drawing Page(s)
LINE COUNT: 12881
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Human TNF-gamma-alpha and TNF-gamma-beta polypeptides and DNA (RNA) encoding such polypeptides and a procedure for producing such polypeptides by recombinant techniques are disclosed. Also disclosed are methods for utilizing such polypeptides to inhibit cellular growth, for example in a tumor or cancer, for facilitating wound-healing, to provide resistance against infection, induce inflammatory activities, and stimulating the growth of certain cell types to treat diseases, for example restenosis. Also disclosed are diagnostic methods for detecting a mutation in the TNF-gamma-alpha and TNF-gamma-beta nucleic acid sequences or overexpression of the TNF-gamma-alpha and/or TNF-gamma-beta polypeptides. Antagonists against such polypeptides and their use as a therapeutic to treat cachexia, septic shock, cerebral malaria, inflammation, arthritis and graft-rejection are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 25 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2002:171934 USPATFULL
TITLE: TUMOR NECROSIS FACTOR-GAMMA
INVENTOR(S): YU, GUO-LIANG, SAN MATEO, CA, UNITED STATES
NI, JIAN, ROCKVILLE, MD, UNITED STATES
ROSEN, CRAIG A., LAYTONSVILLE, MD, UNITED STATES
ZHANG, JUN, BETHESDA, MD, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002090683	A1	20020711	<--
	US 6824767	B2	20041130	
APPLICATION INFO.:	US 1999-246129	A1	19990208 (9)	

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-131237, filed on 7 Aug 1998, PENDING Continuation-in-part of Ser. No. US 1998-5020, filed on 9 Jan 1998, ABANDONED Continuation-in-part of Ser. No. US 1995-461246, filed on 5 Jun 1995, ABANDONED Continuation-in-part of Ser. No. WO 1994-US12880, filed on 7 Nov 1994, UNKNOWN

	NUMBER	DATE

PRIORITY INFORMATION: US 1998-74047P 19980209 (60) <--
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 41
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Page(s)
LINE COUNT: 6959
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Human TNF-gamma-alpha and TNF-gamma-beta polypeptides and DNA (RNA) encoding such polypeptides and a procedure for producing such polypeptides by recombinant techniques is disclosed. Also disclosed are methods for utilizing such polypeptides to inhibit cellular growth, for example in a tumor or cancer, for facilitating wound-healing, to provide resistance against infection, induce inflammatory acitvities, and stimulating the growth of certain cell types to treat diseases, for example restenosis. Also disclosed are diagnostic methods for detecting a mutation in the TNF-gamma-alpha and TNF-gamma-beta nucleic acid sequences or overexperession of the TNF-gamma-alpha and TNF-gamma-beta polypeptides. Antagonists against such polypeptides and their use as a therapeutic to treat cachexia, septic shock, cerebral malaria, inflammation, arthritis and graft-rejection are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 26 OF 34 USPATFULL on STN
ACCESSION NUMBER: 2002:346983 USPATFULL
TITLE: Rin2, a novel inhibitor of Ras-mediated signaling
INVENTOR(S): Tam, See-Ying, Mountain View, CA, United States
Tsai, Mindy, Mountain View, CA, United States
Galli, Stephen J., Portola Valley, CA, United States
PATENT ASSIGNEE(S): Beth Israel Deaconess Medical Center, Palo Alto, CA, United States (U.S. corporation)
The Board of Trustees of the Leland Stanford, Jr., University, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6500942	B1	20021231
APPLICATION INFO.:	US 2000-522955		20000310 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 1998-US19056, filed on 11 Sep 1998 Continuation-in-part of Ser. No. US 1997-942819, filed on 2 Oct 1997, now patented, Pat. No. US 5965707

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-58520P	19970911 (60) <--

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Eyler, Yvonne
ASSISTANT EXAMINER: Nickol, Gary B.
LEGAL REPRESENTATIVE: Hamilton, Brook, Smith & Reynolds, P.C.
NUMBER OF CLAIMS: 45
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Figure(s); 18 Drawing Page(s)
LINE COUNT: 2376
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel gene, rin2, and encoded protein are disclosed which can inhibit the functional response induced by Ras-dependent signaling pathways are disclosed. Methods of inhibiting or enhancing Ras-dependent signaling and methods of treatment utilizing Rin2 are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 27 OF 34 USPATFULL on STN

ACCESSION NUMBER: 2002:181690 USPATFULL

TITLE: Substituted pyrazoles as p38 kinase inhibitors

INVENTOR(S): Anantanarayan, Ashok, Hainesville, IL, United States
Clare, Michael, Skokie, IL, United States
Collins, Paul W., Deerfield, IL, United States
Crich, Joyce Zuowu, Glenview, IL, United States
Devraj, Rajesh, Ballwin, MO, United States
Flynn, Daniel L., Clarkson Valley, MO, United States
Geng, Lifeng, Skokie, IL, United States
Graneto, Matthew J., Chesterfield, MO, United States
Hanau, Cathleen E., Chesterfield, MO, United States
Hanson, Gunnar J., Skokie, IL, United States
Hartmann, Susan J., Kirkwood, MO, United States
Hepperle, Michael, St. Charles, MO, United States
Huang, He, Chicago, IL, United States
Koszyk, Francis J., Prospect Heights, IL, United States
Liao, Shuyuan, Glen Ellyn, IL, United States
Metz, Suzanne, Chesterfield, MO, United States
Partis, Richard A., Evanston, IL, United States
Perry, Thao D., Chesterfield, MO, United States
Rao, Shashidhar N., St. Louis, MO, United States
Selness, Shaun Raj, Chesterfield, MO, United States
South, Michael S., St. Louis, MO, United States
Stealey, Michael A., Libertyville, IL, United States
Talley, John Jeffrey, St. Louis, MO, United States
Vazquez, Michael L., Ballwin, MO, United States
Weier, Richard M., Lake Bluff, IL, United States
Xi, Xiangdong, Evanston, IL, United States
Khanna, Ish K., Libertyville, IL, United States
Yu, Yi, Skokie, IL, United States

PATENT ASSIGNEE(S): G. D. Searle & Company, Skokie, IL, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6423713	B1	20020723
APPLICATION INFO.:	US 2001-918481		20010731 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1998-196623, filed on 20 Nov 1998 Continuation-in-part of Ser. No. US 1998-83670, filed on 22 May 1998, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-47570P	19970522 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Solola, T. A.
LEGAL REPRESENTATIVE: Harness, Dickey & Pierce, P.L.C.
NUMBER OF CLAIMS: 88
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 16941

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A class of pyrazole derivatives is described for use in treating p38 kinase mediated disorders. Compounds of particular interest are defined by Formula IA ##STR1##

wherein R.sup.1, R.sup.2, R.sup.3 and R.sup.4 are as described in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 28 OF 34 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:742981 HCAPLUS
DOCUMENT NUMBER: 138:53701
TITLE: p38 and Activating Transcription Factor-2 Involvement in Osteoblast Osmotic Response to Elevated Extracellular Glucose
AUTHOR(S): Zayzafoon, Majd; Botolin, Sergiu; McCabe, Laura R.
CORPORATE SOURCE: Department of Physiology, Michigan State University, East Lansing, MI, 48824, USA
SOURCE: Journal of Biological Chemistry (2002), 277(40), 37212-37218
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Poorly controlled or untreated **type I diabetes** mellitus is characterized by hyperglycemia and is associated with decreased bone mass and osteoporosis. We have demonstrated that osteoblasts are sensitive to hyperglycemia-associated osmotic stress and respond to elevated extracellular glucose or mannitol by increasing c-jun and collagen I expression. To determine whether MAPKs are involved in this response, MC3T3-E1 osteoblasts were treated with 16.5 mm glucose, mannitol, or contrast dye for 1 h. Immunoblotting of phosphorylated p38 demonstrated activation of p38 MAPK by hyperosmotic stress in vitro and in vivo. Activation peaked at 20 min, remained detectable after 24 h, and was protein kinase C-independent. Activating transcription factor-2 (ATF-2) activation followed the same pattern as phospho-p38. Transactivation of cAMP response element (CRE)- and c-jun promoter (containing a CRE-like element)-reporter constructs increased following hyperosmotic treatment. SB 203580 (a **p38 MAPK inhibitor**) blocked ATF-2 phosphorylation, CRE transactivation, and c-jun promoter activation. Hyperosmotic activation of collagen I promoter activity was also inhibited by SB 203580, consistent with the involvement of c-jun in collagen I up-regulation. Therefore, we propose that hyperglycemia-induced increases in p38 MAPK activity and ATF-2 phosphorylation contribute to CRE activation and modulation of c-jun and collagen I expression in osteoblasts.

REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 29 OF 34 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:521726 HCAPLUS
DOCUMENT NUMBER: 137:214971
TITLE: Hyperketonemia increases tumor necrosis factor-α secretion in cultured U937 monocytes and type 1 diabetic patients and is apparently mediated by oxidative stress and cAMP deficiency
AUTHOR(S): Jain, Sushil K.; Kannan, Krishnaswamy; Lim, Gideon; McVie, Robert; Bocchini, Joseph A., Jr.

CORPORATE SOURCE: Department of Pediatrics, Louisiana State University Health Sciences Center, Shreveport, LA, 71130, USA
SOURCE: Diabetes (2002), 51(7), 2287-2293
CODEN: DIAEAZ; ISSN: 0012-1797
PUBLISHER: American Diabetes Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An elevated blood level of tumor necrosis factor (TNF)-α is a validated marker of vascular inflammation, which can result in the development of vascular disease and atherosclerosis. This study examined the hypothesis that ketosis increases the TNF-α secretion, both in a cell culture model using U937 monocytes and in type 1 diabetic patients in vivo. U937 cells were cultured with ketone bodies (acetoacetate [AA] and β-hydroxybutyrate [BHB]) in the presence or absence of high levels of glucose in medium at 37° for 24 h. This study demonstrates the following points. First, hyperketonemic diabetic patients have significantly higher levels of TNF-α than normoketonemic diabetic patients ($P < 0.01$) and normal control subjects ($P < 0.01$). There was a significant correlation ($r = 0.36$, $P < 0.05$; $n = 34$) between ketosis and oxidative stress as well as between oxidative stress and TNF-α levels ($r = 0.47$, $P < 0.02$; $n = 34$) in the blood of diabetic patients. Second, ketone body AA treatment increases TNF-α secretion, increases oxygen radicals production, and lowers cAMP levels in U937 cells. However, BHB did not have any effect on TNF-α secretion or oxygen radicals production in U937 cells. Third, exogenous addition of dibutyryl cAMP, endogenous stimulation of cAMP production by forskolin, and antioxidant N-acetylcysteine (NAC) prevented stimulation of TNF-α secretion caused by AA alone or with high glucose. Similarly, NAC prevented the elevation of TNF-α secretion and lowering of cAMP levels in H2O2-treated U937 cells. Fourth, the effect of AA on TNF-α secretion was inhibited by specific inhibitors of protein kinase A (H89), p38-mitogen-activated protein kinase (SB203580), and nuclear transcription factor (NFκB) (NFκB-SN50). This study demonstrates that hyperketonemia increases TNF-α secretion in cultured U937 monocytic cells and TNF-α levels in the blood of type 1 diabetic patients and is apparently mediated by AA-induced cellular oxidative stress and cAMP deficiency.

L24 ANSWER 30 OF 34 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:870187 HCAPLUS
DOCUMENT NUMBER: 136:132847
TITLE: A role for mitogen-activated protein kinases in the etiology of diabetic neuropathy
AUTHOR(S): Purves, Tertia; Middlemas, Alicia; Agthong, Sithiporn; Jude, Edward B.; Boulton, Andrew J. M.; Fernyhough, Paul; Tomlinson, David R.
CORPORATE SOURCE: Neuroscience Division, School of Biological Sciences, University of Manchester, Manchester, UK
SOURCE: FASEB Journal (2001), 15(13), 2508-2514
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The onset of diabetic neuropathy, a complication of **diabetes** mellitus, has been linked to poor glycemic control. We tested the hypothesis that the mitogen-activated protein kinases (MAPK) form transducers for the damaging effects of high glucose. In cultures of adult rat sensory neurons, high glucose activated JNK and p38 MAPK but did

not result in cell damage. However, oxidative stress activated ERK and p38 MAPKs and resulted in cellular damage. In the dorsal root ganglia of streptozotocin-induced diabetic rats (a model of **type I diabetes**), ERK and p38 were activated at 8 wk duration, followed by activation of JNK at 12 wk duration. We report activation of JNK and increases in total levels of p38 and JNK in sural nerve of type I and II diabetic patients. These data implicate MAPKs in the etiol. of diabetic neuropathy both via direct effects of glucose and via glucose-induced oxidative stress.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 31 OF 34 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:154506 HCAPLUS
DOCUMENT NUMBER: 135:370453
TITLE: Monocyte chemoattractant protein-1 is expressed in pancreatic islets from prediabetic NOD mice and in interleukin-1β-exposed human and rat islet cells
AUTHOR(S): Chen, M.-C.; Proost, P.; Gysemans, C.; Mathieu, C.; Eizirik, D. L.
CORPORATE SOURCE: Gene Expression Unit, Diabetes Research Center, Vrije Universiteit Brussel, Brussels, Belg.
SOURCE: Diabetologia (**2001**), 44(3), 325-332
CODEN: DBTGAJ; ISSN: 0012-186X
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Monocyte chemoattractant protein-1 (MCP-1) attracts monocytes and T lymphocytes, and could thus contribute to mononuclear cell infiltration in type I (insulin-dependent) **diabetes** mellitus. Cytokines induce MCP-1 mRNA expression in pancreatic rat β cells. To investigate this issue, the authors analyzed the signal transduction for IL-1β-induced MCP-1 expression in rat β cells and in vitro MCP-1 mRNA expression and protein release by human islets as well as in vivo islet MCP-1 mRNA expression in prediabetic non-obese diabetic mice. Fluorescence-activated cell sorting-purified rat β cells were cultured for 6 h with IL-1β (30 U/mL) or MAPK inhibitors or both. Human islets were cultured for 6-72 h with the cytokines IL-1β, IFN-γ, or the inducible nitric oxide synthase (iNOS) inhibitor NG-methyl-L-arginine or both. The authors measured MCP-1 mRNA by RT-PCR and protein by ELISA. The MCP-1 mRNA expression in islets from male and female non-obese diabetic mice (2-12 wk of age) was measured by real time reverse transcription-polymerase chain reaction (RT-PCR). Interleukin-1β induced MCP-1 mRNA expression in rat β cells, with a maximum induction after 6 h. A combination of p38 and ERK1/2 inhibitors decreased MCP-1 expression by 70%. IL-1β induced both MCP-1 mRNA expression and a 3-fold increase in medium MCP-1 protein accumulation in human islet cells. This effect was not prevented by iNOS blockers. In vivo there was an age-related increase in MCP-1 mRNA expression in islets from male and female non-obese diabetic mice, reaching a peak at 8 wk. Thus, in rat and human islet cells MCP-1 mRNA is induced by IL-1β. Both ERK1/2 and p38 MAPK, but not nitric oxide, contribute to MCP-1 expression. In non-obese diabetic mice MCP-1 mRNA expression increases with age, peaking at the early phases of insulitis. The production of MCP-1 by pancreatic beta cells could contribute to the recruitment of mononuclear cells into pancreatic islets in early **Type I diabetes.**

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 32 OF 34 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:506695 HCAPLUS
DOCUMENT NUMBER: 136:83924
TITLE: Increased cytokine-induced cytotoxicity of pancreatic islet cells from transgenic mice expressing the Src-like tyrosine kinase GTK
AUTHOR(S): Anneren, Cecilia; Welsh, Michael
CORPORATE SOURCE: Department of Medical Cell Biology, Uppsala University, Uppsala, Swed.
SOURCE: Molecular Medicine (Baltimore, MD, United States) (**2001**), 7(5), 301-310
CODEN: MOMEF3; ISSN: 1076-1551
PUBLISHER: Johns Hopkins University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The loss of β cells in **type 1 diabetes** may involve protein kinases because they control cell growth, differentiation, and survival. Previous studies have revealed that GTK, a Src-like protein tyrosine kinase expressed in β cells (also named Bsk/Iyk), regulates multiple responses including growth and survival of rat insulinoma cells (RINm5F) and differentiation of neuronal PC12 cells. In the present study, the authors have generated a transgenic mouse expressing a kinase active GTK mutant (GTK-Y504F) under the control of the rat insulin I promoter to establish a role of GTK in β cells. Control and GTK-transgenic CBA mice were used for determination of in vivo glucose tolerance and the relative insulin-pos. area. Isolated islets from both groups were cultured in the absence and presence of cytokines and insulin secretion, viability and protein expression were assessed. The β-cell mass of GTK-transgenic mice was increased as a consequence of a larger pancreas and an increased relative β-cell area. Islets isolated from the transgenic animals exhibited an enhanced glucose-induced insulin release and reduced viability in response to cytokines that could not be explained by higher levels of NO compared with control islets. Extra-cellular signal-regulated kinase (ERK) 1/2, p38 mitogen-activated protein kinase (MAPK), c-Jun NH2-terminal kinase (JNK), and Akt were all activated by cytokines, but GTK-transgenic islets contained higher basal levels of phosphorylated ERK1/2 and lower basal levels of phosphorylated p38 compared with the control islets. The total amount of activated MAPKs was, however, higher in the cytokine-stimulated transgenic islets compared with the control islets due to increased levels of phospho-ERK1/2. Moreover, the proline-rich tyrosine kinase (PYK) 2 (also named RAFTK/CAK β/CADTK) levels were elevated in response to a 24-h exposure to cytokines in control islets but not in the GTK-transgenic islets. These results suggest that although GTK increases the β-cell mass, it also enhances islet cell death in response to cytokines and may thus be involved in the β-cell damage in **type 1 diabetes.**
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 33 OF 34 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:627254 HCAPLUS
DOCUMENT NUMBER: 133:295222
TITLE: Activation of extracellular signal-regulated kinase (ERK) 1/2 contributes to cytokine-induced apoptosis in purified rat pancreatic β-cells
AUTHOR(S): Pavlovic, Dejan; Andersen, Nina Aa.; Mandrup-Poulsen, Thomas; Eizirik, Decio L.
CORPORATE SOURCE: Gene Expression Unit Diabetes Research Center, Vrije Universiteit Brussel, Brussels, B-1090, Belg.

SOURCE: European Cytokine Network (2000), 11(2), 267-274
CODEN: ECYNEJ; ISSN: 1148-5493
PUBLISHER: John Libbey Eurotext
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cytokines may contribute to β-cell apoptosis in the early stages of **type 1 diabetes** mellitus. It has been reported recently that interleukin-1β (IL-1β) induces activation of the mitogen-activated protein kinases (MAPK) p38 and ERK1/2 in neonatal rat islets. Since these kinases may participate in cytokine-induced apoptosis, we evaluated whether cytokines induce activation of MAPKs in FACS-purified primary rat β-cells, and whether blockers of p38 and/or ERK1/2 prevent β-cell death. IL-1β, but not interferon-γ (IFN-γ), caused phosphorylation of the substrates Elk-1, ATF-2 and hsp25, and the phosphorylation of both Elk-1 and hsp25 were decreased by the p38 blocker SB203580 (p38i) and the MAPK/ERK blocker PD 098059 (MEKi). When added together, p38i and MEKi decreased IL-1β-induced nitrite production over 24 h by 60%, but did not affect IL-1β-induced manganese superoxide dismutase (MnSOD) mRNA expression. To test the effects of MAPK inhibitors on β-cell death by necrosis or apoptosis, these cells were exposed for 6 or 9 days to IL-1β + IFN-γ. This treatment induced cell death, mostly by apoptosis. The MEKi, but not the p38i, significantly decreased cytokine-induced apoptosis, thus decreasing the total number of dead cells. This protection was only partial, suggesting that ERK1/2 activation is not the only mechanism by which cytokines induce β-cell apoptosis. We conclude that IL-1β induces activation of both p38 and ERK1/2, and that ERK1/2 contributes to the pro-apoptotic effects of the cytokine in primary β-cells.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 34 OF 34 USPATFULL on STN
ACCESSION NUMBER: 1999:125043 USPATFULL
TITLE: Rin2, a novel inhibitor of Ras-mediated signaling
INVENTOR(S): Tam, See-Ying, Wellesley, MA, United States
Tsai, Mindy, Wellesley, MA, United States
Galli, Stephen J., Winchester, MA, United States
PATENT ASSIGNEE(S): Beth Israel Deaconess Medical Center, Boston, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5965707		19991012	<--
APPLICATION INFO.:	US 1997-942819		19971002	(8)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1997-58520P	19970911 (60)	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Hutzell, Paula K.
ASSISTANT EXAMINER: Sun-Hoffman, Lin
LEGAL REPRESENTATIVE: Hamilton, Brook, Smith & Reynolds, P.C.
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT: 1882
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel gene, rin2, and encoded protein are disclosed which can inhibit

the functional response induced by Ras-dependent signaling pathways are disclosed. Methods of inhibiting or enhancing Ras-dependent signaling and methods of treatment utilizing Rin2 are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TEXT SEARCH - MEDLINE BIOSIS EMBASE JAPIO JICST

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=> d que stat l22
L17           2 SEA FILE=REGISTRY ABB=ON  ("P38 MAPK"/CN OR "P38 MAPK (BIOMPHAL
                ARIA GLABRATA STRAIN BS90 HEMOCYTE)"/CN OR "P38 MAPK INHIBITOR"
                /CN)
L18       10002 SEA FILE=HCAPLUS ABB=ON  L17 OR P38(W)?MAPK?(W)?INHIBIT?
L19         320 SEA FILE=HCAPLUS ABB=ON  L18 AND ?DIABETES?
L20          25 SEA FILE=HCAPLUS ABB=ON  L19 AND (TYPE(W)(1 OR I)(W)?DIABETES?)
L22          23 SEA L20

=> d ibib abs l22 1-23

L22  ANSWER 1 OF 23     MEDLINE on STN
ACCESSION NUMBER:   2002493287     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 12149242
TITLE:              P38 and activating transcription factor-2 involvement in
                    osteoblast osmotic response to elevated extracellular
                    glucose.
AUTHOR:             Zayzafoon Majd; Botolin Sergiu; McCabe Laura R
CORPORATE SOURCE:   Department of Physiology, Michigan State University, East
                    Lansing, Michigan 48824, USA.
SOURCE:             The Journal of biological chemistry, (2002 Oct 4) Vol. 277,
                    No. 40, pp. 37212-8.  Electronic Publication: 2002-07-30.
                    Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200211
ENTRY DATE:         Entered STN: 1 Oct 2002
                    Last Updated on STN: 5 Jan 2003
                    Entered Medline: 20 Nov 2002
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AB Poorly controlled or untreated **type I diabetes** mellitus is characterized by hyperglycemia and is associated with decreased bone mass and osteoporosis. We have demonstrated that osteoblasts are sensitive to hyperglycemia-associated osmotic stress and respond to elevated extracellular glucose or mannitol by increasing c-jun and collagen I expression. To determine whether MAPKs are involved in this response, MC3T3-E1 osteoblasts were treated with 16.5 mm glucose, mannitol, or contrast dye for 1 h. Immunoblotting of phosphorylated p38 demonstrated activation of p38 MAPK by hyperosmotic stress in vitro and in vivo. Activation peaked at 20 min, remained detectable after 24 h, and was protein kinase C-independent. Activating transcription factor-2 (ATF-2) activation followed the same pattern as phospho-p38. Transactivation of cAMP response element (CRE)- and c-jun promoter (containing a CRE-like element)-reporter constructs increased following hyperosmotic treatment. SB 203580 (a **p38 MAPK inhibitor**) blocked ATF-2 phosphorylation, CRE transactivation, and c-jun promoter activation. Hyperosmotic activation of collagen I promoter activity was also inhibited by SB 203580, consistent with the involvement of c-jun in collagen I up-regulation. Therefore, we propose that hyperglycemia-induced increases in p38 MAPK activity and ATF-2 phosphorylation contribute to CRE activation and modulation of c-jun and collagen I expression in osteoblasts.

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L22  ANSWER 2 OF 23  BIOSIS  COPYRIGHT (c) 2006 The Thomson Corporation  on STN
ACCESSION NUMBER:   2006:453398  BIOSIS
DOCUMENT NUMBER:    PREV200600449427
TITLE:              Insulin signal mimicry as a mechanism for the insulin-like
```

effects of vanadium.
AUTHOR(S): Mehdi, Mohamad Z.; Pandey, Sanjay K.; Theberge, Jean-Francois; Srivastava, Ashok K. [Reprint Author]
CORPORATE SOURCE: CHU Montreal, Hotel Dieu, Lab Cell Signaling, Res Ctr, Montreal, PQ, Canada
ashok.srivastava@umontreal.ca
SOURCE: Cell Biochemistry and Biophysics, (2006) Vol. 44, No. 1, pp. 73-81.
ISSN: 1085-9195.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Sep 2006
Last Updated on STN: 13 Sep 2006

AB Among several metals, vanadium has emerged as an extremely potent agent with insulin-like properties. These insulin-like properties have been demonstrated in isolated cells, tissues, different animal models of type I and type II **diabetes** as well as a limited number of human subjects. Vanadium treatment has been found to improve abnormalities of carbohydrate and lipid metabolism and of gene expression in rodent models of **diabetes.** In isolated cells, it enhances glucose transport, glycogen and lipid synthesis, and inhibits gluconeogenesis and lipolysis. The molecular mechanism responsible for the insulin-like effects of vanadium compounds have been shown to involve the activation of several key components of insulin-signaling pathways that include the mitogen-activated-protein kinases (MAPKs) extracellular signal-regulated kinase 1/2 (ERK1/2) and p38NIAPK, and phosphaticlylinositol 3-kinase (PI3-K)/protein kinase B (PKB). It is interesting that the vanadium effect on these signaling systems is independent of insulin receptor protein tyrosine kinase activity, but it is associated with enhanced tyrosine phosphorylation of insulin receptor substrate-1. These actions seem to be secondary to vanadium-induced inhibition of protein tyrosine phosphatases. Because MAPK and PI3-K/PKB pathways are implicated in mediating the mitogenic and metabolic effects of insulin, respectively, it is plausible that mimicry of these pathways by vanadium serves as a mechanism for its insulin-like responses.

L22 ANSWER 3 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:412874 BIOSIS
DOCUMENT NUMBER: PREV200600415391
TITLE: Elevated glucose and **diabetes** promote interleukin-12 cytokine gene expression in mouse macrophages.
AUTHOR(S): Wen, Yeshao; Gu, Jiali; Li, Shu-Lian; Reddy, Marpadga A.; Natarajan, Rama; Nadler, Jerry L. [Reprint Author]
CORPORATE SOURCE: Univ Virginia, Diabet and Hormone Ctr, Charlottesville, VA 22908 USA
jln2n@virginia.edu
SOURCE: Endocrinology, (MAY 2006) Vol. 147, No. 5, pp. 2518-2525.
CODEN: ENDOAO. ISSN: 0013-7227.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Aug 2006
Last Updated on STN: 23 Aug 2006

AB Inflammation is emerging as an important mechanism for microand macrovascular complication of **diabetes.** The macrophage plays a key role in the chronic inflammatory response in part by generating particular cytokines. IL-1 beta, IL-6, IL12, IL-18, TNF alpha, and interferon-gamma are produced primarily in macrophages and have been associated with accelerated atherosclerosis and altered vascular wall

function. In this study, we evaluated the effect and mechanism of high glucose (HG) on gene expression of these cytokines in mouse peritoneal macrophages (MPM). HG led to a 2-fold increase in the mRNA expression of these cytokines, with IL-12 showing the highest activation (5.4-fold) in a time-dependent (3-12 h) and dosedependent (10, 17.5, and 25 mmol/liter) manner. The effects were specific to HG because mannitol and 3-O-methyl-glucose had no effect on cytokine mRNA expression. HG also increased IL-12 protein accumulation from MPM. We also explored the role of induced and spontaneous **diabetes** on inflammatory cytokine expression in MPM. Increases in expression in MPM of multiple inflammatory cytokines, including a 20-fold increase in IL-12 mRNA, were observed in streptozotocin- induced type 1 diabetic mice as well as type 2 diabetic db/db mice, suggesting that cytokine gene expression is increased by hyperglycemia in vivo. We next explored potential mechanisms of HG-induced increases in IL-12 mRNA. HGincreased the activity of protein kinase C, p38MAPK (p38), c-Jun terminal kinase, and inhibitory-kappa B kinase in MPM. Furthermore, inhibitors of these signaling pathways significantly reduced HG-induced IL-12 mRNA expression in MPM. These results provide evidence for a potentially important mechanism linking elevated glucose and **diabetes** to inflammation.

L22 ANSWER 4 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:351802 BIOSIS
DOCUMENT NUMBER: PREV200600364780
TITLE: Defective NF-kappaB activation in response to LPS in **type 1 diabetes** dendritic cells.
AUTHOR(S): Mollah, Z. U. A. [Reprint Author]; Moore, C.; Sullivan, B.; Peng, J.; Phillips, K.; Cardinal, J.; Prins, J.; Thomas, R.
CORPORATE SOURCE: Ctr Immunol and Canc Res, Buranda, Qld, Australia
SOURCE: Tissue Antigens, (NOV 2005) Vol. 66, No. 5, pp. 496. Meeting Info.: 35th Annual Scientific Meeting of the Australasian-Society-for-Immunology/14th International HLA and Immunogenetics Workshops. Melbourne, AUSTRALIA. November 29 -December 02, 2005. Australasian Soc Immunol. CODEN: TSANA2. ISSN: 0001-2815.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Jul 2006
Last Updated on STN: 19 Jul 2006

L22 ANSWER 5 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:179259 BIOSIS
DOCUMENT NUMBER: PREV200600161409
TITLE: Glucose-induced reactive oxygen species cause apoptosis of podocytes and podocyte depletion at the onset of diabetic nephropathy.
AUTHOR(S): Susztak, Katalin; Raff, Amanda C.; Schiffer, Mario; Boettinger, Erwin P. [Reprint Author]
CORPORATE SOURCE: Mt Sinai Sch Med, Div Nephrol, Dept Med, 1 Gustave L Levy Pl, New York, NY 10029 USA
ksusztak@aecom.yu.edu
SOURCE: Diabetes, (JAN 2006) Vol. 55, No. 1, pp. 225-233. CODEN: DIAEAZ. ISSN: 0012-1797.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Mar 2006
Last Updated on STN: 9 Mar 2006
AB Diabetic nephropathy is the most common cause of end-stage renal disease

in the U.S. Recent studies demonstrate that loss of podocytes is an early feature of diabetic nephropathy that predicts its progressive course. Cause and consequences of podocyte loss during early diabetic nephropathy remain poorly understood. Here, we demonstrate that podocyte apoptosis increased sharply with onset of hyperglycemia in Ins2(Akita) (Akita) mice with **type 1 diabetes** and Lepr(db/db) (db/db) mice with obesity and type 2 **diabetes.** Podocyte apoptosis coincided with the onset of urinary albumin excretion (UAE) and preceded significant losses of podocytes in Akita (37% reduction) and db/db (27% reduction) mice. Increased extracellular glucose (30 mmol/l) rapidly stimulated generation of intracellular reactive oxygen species (ROS) through NADPH oxidase and mitochondrial pathways and led to activation of proapoptotic p38 mitogen-activated protein kinase and caspase 3 and to apoptosis of conditionally immortalized podocytes in vitro. Chronic inhibition of NADPH oxidase prevented podocyte apoptosis and ameliorated podocyte depletion, UAE, and mesangial matrix expansion in db/db mice. In conclusion, our results demonstrate for the first time that glucose-induced ROS production initiates podocyte apoptosis and podocyte depletion in vitro and in vivo and suggest that podocyte apoptosis/depletion represents a novel early pathomechanism(s) leading to diabetic nephropathy in murine type 1 and type 2 diabetic models.

L22 ANSWER 6 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:155490 BIOSIS
DOCUMENT NUMBER: PREV200600163314
TITLE: The inflammatory chemokine, interferon-gamma-inducible protein (IP-10), is induced in monocytes by ligands of the receptor for advanced glycation end products (RAGE).
AUTHOR(S): Shanmugam, Narkunaraja [Reprint Author]; Ransohoff, Richard M.; Natarajan, Rama
SOURCE: Diabetes, (JUN 2004) Vol. 53, No. Suppl. 2, pp. A450. Meeting Info.: 64th Annual Meeting of the American-Diabetes-Association. Orlando, FL, USA. June 04 -08, 2004. Amer Diabet Assoc.
CODEN: DIAEAZ. ISSN: 0012-1797.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Mar 2006
Last Updated on STN: 9 Mar 2006

L22 ANSWER 7 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:474184 BIOSIS
DOCUMENT NUMBER: PREV200510274945
TITLE: Effects of sodium tungstate in Min6 beta-cells: potential implications for its antidiabetic action.
AUTHOR(S): Piquer, S. [Reprint Author]; Barcelo-Batllori, S.; Julia, M.; Gomis, R.
CORPORATE SOURCE: Hosp Clin Barcelona, Lab Expt Diabet, Barcelona, Spain
SOURCE: Diabetologia, (AUG 2004) Vol. 47, No. Suppl. 1, pp. A169. Meeting Info.: 40th Annual Meeting of the European-Association-for-the-Study-of-Diabetes. Munich, GERMANY. September 05 -09, 2004. European Assoc Study Diabetes.
CODEN: DBTGAJ. ISSN: 0012-186X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Nov 2005
Last Updated on STN: 16 Nov 2005

L22 ANSWER 8 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:402453 BIOSIS
DOCUMENT NUMBER: PREV200510189321
TITLE: Selective inhibition of Fc epsilon RI-mediated mast cell activation by a truncated variant of Cbl-b related to the rat model of **type 1 diabetes** mellitus.
AUTHOR(S): Qu, Xiujuan; Miah, S. M. Shahjahan; Hatani, Tomoko; Okazaki, Mami; Hori-Tamura, Naoko; Yamamura, Hirohei; Hotta, Hak; Sada, Kiyonao [Reprint Author]
CORPORATE SOURCE: Kobe Univ, Grad Sch Med, Dept Genome Sci, Div Proteom, Kobe, Hyogo 6500017, Japan
ksada@med.kobe-u.ac.jp
SOURCE: Journal of Biochemistry (Tokyo), (JUN 2005) Vol. 137, No. 6, pp. 711-720.
CODEN: JOBIAO. ISSN: 0021-924X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Oct 2005
Last Updated on STN: 5 Oct 2005

AB Ubiquitin-protein ligase Cbl-b negatively regulates high affinity IgE receptor (Fc epsilon RI)-mediated degranulation and cytokine gene transcription in mast cells. In this study, we have examined the role of a truncated variant of Cbl-b related to the rat model of **type 1 diabetes** mellitus using the mast cell signaling model. Overexpression of the truncated Cbl-b that lacks the C-terminal region did not suppress the activation of proximal and distal signaling molecules leading to degranulation. Fc epsilon CRI-mediated tyrosine phosphorylation of Syk, Gab2, and phospholipase C-gamma 1, and activation of c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinase (MAP kinase), and inhibitor of nuclear factor kappa B kinase (IKK), and generation of Rac1 are unaffected in cells overexpressing the truncated Cbl-b in the lipid raft. On the other hand, Fc epsilon RI-mediated transcriptional activation of nuclear factor of activated T cells (NFAT), and transcription of interleukin-3 (IL-3) and IL-4 mRNA are inhibited by overexpression of the truncated variant of Cbl-b. This suppression parallels the re-compartmentalization of specific effector molecules in the lipid raft. These structural and functional analyses reveal the mechanism underlying the selective inhibition of cellular signaling by the truncated variant of Cbl-b related to insulin-dependent **diabetes** mellitus.

L22 ANSWER 9 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:123865 BIOSIS
DOCUMENT NUMBER: PREV200500129411
TITLE: C-peptide stimulates ERK1/2 and JNK MAP kinases via activation of protein kinase C in human renal tubular cells.
AUTHOR(S): Zhong, Z.; Davidescu, A.; Ehren, I.; Ekberg, K.; Jornvall, H.; Wahren, J.; Chibalin, A. V. [Reprint Author]
CORPORATE SOURCE: Dept Surg SciSect Integrat Physiol, Karolinska Inst, von Eulers Vag 4,4 Tr, S-17177, Stockholm, Sweden
Alexander.Chibalin@kirurgi.ki.se
SOURCE: Diabetologia, (January 2005) Vol. 48, No. 1, pp. 187-197. print.
CODEN: DBTGAJ. ISSN: 0012-186X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Apr 2005

Last Updated on STN: 1 Apr 2005

AB Aims/hypothesis: Accumulating evidence indicates that replacement of C-peptide in **type 1 diabetes** ameliorates nerve and kidney dysfunction, but the molecular mechanisms involved are incompletely understood. C-peptide shows specific binding to a G-protein-coupled membrane binding site, resulting in Ca2+ influx, activation of mitogen-activated protein kinase signalling pathways, and stimulation of Na+, K+-ATPase and endothelial nitric oxide synthase. This study examines the intracellular signalling pathways activated by C-peptide in human renal tubular cells. Methods: Human renal tubular cells were cultured from the outer cortex of renal tissue obtained from patients undergoing elective nephrectomy. Extracellular-signal- regulated kinase 1/2 (ERK1/2), c-Jun N-terminal kinase (JNK) and Akt/protein kinase B (PKB) activation was determined using phospho-specific antibodies. Protein kinase C (PKC) and RhoA activation was determined by measuring their translocation to the cell membrane fraction using isoform-specific antibodies. Results: Human C-peptide increases phosphorylation of ERK1/2 and Akt/PKB in a concentration- and time-dependent manner in renal tubular cells. The C-terminal pentapeptide of C-peptide is equipotent with the full-length C-peptide, whereas scrambled C-peptide has no effect. C-peptide stimulation also results in phosphorylation of JNK, but not of p38 mitogen-activated protein kinase. MEK1/2 inhibitor PD98059 blocks the C-peptide effect on ERK1/2 phosphorylation. C-peptide causes specific translocation of PKC isoforms delta and epsilon to the membrane fraction in tubular cells. All stimulatory effects of C-peptide were abolished by pertussis toxin. The isoform-specific PKC-delta inhibitor rottlerin and the broad-spectrum PKC inhibitor GF109203X both abolish the C-peptide effect on ERK1/2 phosphorylation. C-peptide stimulation also causes translocation of the small GTPase RhoA from the cytosol to the cell membrane. Inhibition of phospholipase C abolished the stimulatory effect of C-peptide on phosphorylation of ERK1/2, JNK and PKC-delta. Conclusions/interpretation: C-peptide signal transduction in human renal tubular cells involves the activation of phospholipase C and PKC-delta and PKC-epsilon, as well as RhoA, followed by phosphorylation of ERK1/2 and JNK, and a parallel activation of Akt.

L22 ANSWER 10 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:425620 BIOSIS
DOCUMENT NUMBER: PREV200400422623
TITLE: Abnormal p38 mitogen-activated protein kinase signalling in human and experimental diabetic nephropathy.
AUTHOR(S): Adhikary, L.; Chow, F.; Nikolic-Paterson, D. J.; Stambe, C.; Dowling, J.; Atkins, R. C.; Tesch, G. H. [Reprint Author]
CORPORATE SOURCE: Dept Nephrol, Monash Med Ctr, 246 Clayton Rd, Clayton, Vic, 3168, Australia
gtesch@hotmail.com
SOURCE: Diabetologia, (July 2004) Vol. 47, No. 7, pp. 1210-1222. print.
CODEN: DBTGAJ. ISSN: 0012-186X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Nov 2004
Last Updated on STN: 3 Nov 2004

AB Aims/hypothesis. Inflammation and fibrosis are pathological mechanisms that are partially regulated by cell signalling through the p38 mitogen-activated protein kinase (MAPK) pathway. Elements of the diabetic milieu such as high glucose and advanced glycation end-products induce activation of this pathway in renal cells. Therefore, we examined whether

p38 MAPK signalling is associated with the development of human and experimental diabetic nephropathy. Methods. Immunostaining identified phosphorylated (active) p38 MAPK in human biopsies with no abnormality (n=6) and with Type 2 diabetic nephropathy (n=12). Changes in kidney levels of phosphorylated p38 were assessed by immunostaining and western blotting in mice with streptozotocin-induced **Type 1 diabetes** that had been killed after 0.5, 2, 3, 4 and 8 months, and in Type 2 diabetic db/db mice at 2, 4, 6 and 8 months of age. Results. Phosphorylated p38 was detected in some intrinsic cells in normal human kidney, including podocytes, cortical tubules and occasional interstitial cells. Greater numbers of these phosphorylated p38+ cells were observed in diabetic patients, and phosphorylated p38 was identified in accumulating interstitial macrophages and myofibroblasts. A similar pattern of p38 activation was observed in both mouse models of **diabetes.** In mice, kidney levels of phosphorylated p38 increased (2-6 fold) following the onset of Type 1 and Type 2 **diabetes.** In both mouse models, interstitial phosphorylated p38+ cells were associated with hyperglycaemia, increased HbA1c levels and albuminuria. Further assessment of streptozotocin-induced diabetic nephropathy showed that interstitial phosphorylated p38+ cells correlated with interstitial fibrosis (myofibroblasts, collagen). Conclusions/interpretation. Increased p38 MAPK signalling is a feature of human and experimental diabetic nephropathy. Time course studies in mouse models suggest that phosphorylation of p38 plays a pathological role, particularly in the development of interstitial fibrosis.

L22 ANSWER 11 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:178316 BIOSIS
DOCUMENT NUMBER: PREV200400179575
TITLE: Molecular mechanisms of high glucose-induced cyclooxygenase-2 expression in monocytes.
AUTHOR(S): Shanmugam, Narkunaraja; Gaw Gonzalo, Irene T.; Natarajan, Rama [Reprint Author]
CORPORATE SOURCE: Department of Diabetes, Beckman Research Institute of City of Hope, 1500 East Duarte Rd., Duarte, CA, 91010, USA rnatarajan@coh.org
SOURCE: Diabetes, (March 2004) Vol. 53, No. 3, pp. 795-802. print. ISSN: 0012-1797 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Mar 2004
Last Updated on STN: 31 Mar 2004

AB The cyclooxygenase (COX)-2 enzyme has been implicated in the pathogenesis of several inflammatory diseases. However, its role in diabetic vascular disease is unclear. In this study, we evaluated the hypothesis that diabetic conditions can induce COX-2 in monocytes. High glucose treatment of THP-1 monocytic cells led to a significant three- to fivefold induction of COX-2 mRNA and protein expression but not COX-1 mRNA. High glucose-induced COX-2 mRNA was blocked by inhibitors of nuclear factor-kappaB (NF-kappaB), protein kinase C, and p38 mitogen-activated protein kinase. In addition, an antioxidant and inhibitors of mitochondrial superoxide, NADPH oxidase, and glucose metabolism to glucosamine also blocked high glucose-induced COX-2 expression to varying degrees. High glucose significantly increased transcription from a human COX-2 promoter-luciferase construct (twofold, $P < 0.001$). Promoter deletion analyses and inhibition of transcription by NF-kappaB superrepressor and cAMP-responsive element binding (CREB) mutants confirmed the involvement of NF-kappaB and CREB transcription factors in high glucose-induced COX-2 regulation. In addition, isolated peripheral

blood monocytes from type 1 and type 2 diabetic patients had high levels of COX-2 mRNA, whereas those from normal volunteers showed no expression. These results show that high glucose and **diabetes** can augment inflammatory responses by upregulating COX-2 via multiple signaling pathways, leading to monocyte activation relevant to the pathogenesis of **diabetes** complications.

L22 ANSWER 12 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:130132 BIOSIS
DOCUMENT NUMBER: PREV200400115748
TITLE: The specific p38 mitogen-activated protein kinase pathway inhibitor FR167653 keeps insulitis benign in nonobese diabetic mice.
AUTHOR(S): Ando, Hitoshi; Kurita, Seiichiro; Takamura, Toshinari [Reprint Author]
CORPORATE SOURCE: Department of Endocrinology and Metabolism, Kanazawa University Graduate School of Medical Science, 13-1 Takara-machi, Kanazawa, Ishikawa, 920-8641, Japan
tt@medf.m.kanazawa-u.ac.jp
SOURCE: Life Sciences, (February 20 2004) Vol. 74, No. 14, pp. 1817-1827. print.
ISSN: 0024-3205 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Mar 2004
Last Updated on STN: 3 Mar 2004

AB The p38 mitogen-activated protein kinase (MAPK) pathway is important in Th1 immunity, macrophage activation, and apoptosis. Since they may be associated with beta-cell destruction during the development of **type 1 diabetes**, we investigated the role of the p38 MAPK pathway in female nonobese diabetic (NOD) mice. Phosphorylated p38 MAPK was observed immunohistochemically in CD4+ cells that had infiltrated into the islets and part of beta-cells, increasing in proportion to the severity of insulitis. Continuous oral administration of 0.08% FR167653, a specific p38 MAPK pathway inhibitor, significantly reduced the ex vivo production of interferon-gamma by splenic Th1 cells without affecting interleukin-4 production by Th2 cells. FR167653 administration from 4-30 weeks of age prevented NOD mice from developing **diabetes** without affecting the severity of insulitis. Treatment with FR167653 after insulitis had developed (i.e. from 10-30 weeks of age) also prevented **diabetes**, further suggesting that treatment with the p38 MAPK pathway inhibitor keeps insulitis benign in NOD mice, partly by inhibiting Th1 immunity. These findings suggest that p38 MAPK is a key mediator that switches insulitis from benign to destructive in the development of **type 1 diabetes.**

L22 ANSWER 13 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:70086 BIOSIS
DOCUMENT NUMBER: PREV200400070419
TITLE: C-peptide enhances insulin-mediated cell growth and protection against high glucose-induced apoptosis in SH-SY5Y cells.
AUTHOR(S): Li, Zhen-guo; Zhang, Weixian; Sima, Anders A. F. [Reprint Author]
CORPORATE SOURCE: Department of Pathology, Wayne State University, 540 East Canfield Ave., Room 9275, H.G. Scott Hall, Detroit, MI, 48201, USA
asima@med.wayne.edu

SOURCE: Diabetes-Metabolism Research and Reviews, (September-October 2003) Vol. 19, No. 5, pp. 375-385. print.
ISSN: 1520-7552 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Feb 2004
Last Updated on STN: 4 Feb 2004

AB Background: We have previously reported that C-peptide exerts preventive and therapeutic effects on diabetic neuropathy in type 1 diabetic BB/Wor-rats and that it prevents duration-dependent hippocampal apoptosis in the same animal model. In the present study, we examined human neuroblastoma SH-SY5Y cells to examine whether C-peptide stimulates cell proliferation/neurite outgrowth and whether it has antiapoptotic effects. Methods: For neurite outgrowth, serum-starved cultures were treated with C-peptide and/or insulin or IGF-1. Neurites were visualized with NF-L antibody and measured morphometrically. Cell numbers were determined using an electronic cell counter. Scrambled C-peptide was used as a negative control. For assessment of apoptosis, SH-SY5Y cells were incubated with 100 mM glucose for 24 h, and the effects of C-peptide and/or insulin or IGF-1 were examined. Apoptosis was demonstrated by transferase-mediated dUTP nick-end labeling (TUNEL)/4,6-diamidino-2-phenylindole (DAPI) stainings, flow cytometry and changes in the expression of Bcl2. Activation of insulin signaling intermediaries was determined by Western blots. Translocation of NF-kappaB was demonstrated immunocytochemically. Results: C-peptide but not scrambled C-peptide stimulated cell proliferation and neurite outgrowth. In the presence of 4 nM insulin, 3 nM C-peptide significantly increased autophosphorylation of the insulin receptor (IR) but not that of the insulin-like growth factor 1 receptor (IGF-1R). It stimulated phosphoinositide 3-kinase (PI-3 kinase) and p38 mitogen-activated protein (MAP) kinase activation, enhanced the expression and translocation of nuclear factor-kappaB (NF-kappaB), promoted the expression of Bcl2 and reduced c-jun N-terminal kinase (JNK) phosphorylation in excess of that of insulin alone. Conclusions: C-peptide in the presence of insulin exerts synergistic effects on cell proliferation, neurite outgrowth and has in the presence of insulin an antiapoptotic effect on high glucose-induced apoptosis but less so on hyperosmolar-induced apoptosis. These effects are likely to be mediated via interactions with the insulin signaling pathway.

L22 ANSWER 14 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:471342 BIOSIS
DOCUMENT NUMBER: PREV200300471342
TITLE: "The matrix unloaded": Implications for cytokine signaling in islets?.
AUTHOR(S): Lowe, William L. Jr. [Reprint Author]
CORPORATE SOURCE: Division of Endocrinology, Metabolism, and Molecular Medicine, Northwestern University, Feinberg School of Medicine, 303 East Chicago Avenue, Tarry 15-703, Chicago, IL, 60611, USA
wlowe@northwestern.edu
SOURCE: Endocrinology, (October 2003) Vol. 144, No. 10, pp. 4262-4263. print.
CODEN: ENDOAO. ISSN: 0013-7227.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Oct 2003
Last Updated on STN: 15 Oct 2003

L22 ANSWER 15 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:459325 BIOSIS
DOCUMENT NUMBER: PREV200300459325
TITLE: **p38 MAPK inhibitor** prevents the development of **type-1 diabetes** and alleviates hyperglycemia in NOD mice: A preliminary report.
AUTHOR(S): Medicherla, Satyanarayana [Reprint Author]; Protter, Andrew [Reprint Author]; Mangadu, Ruban [Reprint Author]; Almirez, Ramona [Reprint Author]; Ma, Jing [Reprint Author]; Dugar, Sundeep [Reprint Author]; Mavunkel, Babu [Reprint Author]; Perumattam, John [Reprint Author]; Schreiner, George [Reprint Author]
CORPORATE SOURCE: Sunnyvale, CA, USA
SOURCE: Diabetes, (2003) Vol. 52, No. Supplement 1, pp. A126-A127. print.
Meeting Info.: 63rd Scientific Sessions of the American Diabetes Association. New Orleans, LA, USA. June 13-17, 2003. American Diabetes Association.
ISSN: 0012-1797 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Oct 2003
Last Updated on STN: 8 Oct 2003

L22 ANSWER 16 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:104749 BIOSIS
DOCUMENT NUMBER: PREV200300104749
TITLE: Methylglyoxal-bovine serum albumin stimulates tumor necrosis factor alpha secretion in RAW 264.7 cells through activation of mitogen-activating protein kinase, nuclear factor kappaB and intracellular reactive oxygen species formation.
AUTHOR(S): Fan, X.; Subramaniam, R.; Weiss, M. F.; Monnier, V. M. [Reprint Author]
CORPORATE SOURCE: Department of Biochemistry, Institute of Pathology, Case Western Reserve University, 2085 Adelbert Road, Cleveland, OH, 41106, USA
vmm3@po.cwru.edu
SOURCE: Archives of Biochemistry and Biophysics, (January 15 2003) Vol. 409, No. 2, pp. 274-286. print.
ISSN: 0003-9861 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Feb 2003
Last Updated on STN: 19 Feb 2003
AB Accumulating evidence suggests that the pathophysiology of **diabetes** is analogous to chronic inflammatory states. Circulating levels of inflammatory cytokines such as IL-6 and tumor necrosis factor alpha (TNFalpha) are increased in both type 1 and type 2 **diabetes** . TNFalpha plays an important role in the pathogenesis of insulin resistance in type 2 **diabetes.** However, the reason for this increase remains unclear. Levels of the dicarbonyl methylglyoxal (MGO) are elevated in diabetic plasma and MGO-modified bovine serum albumin (MGO-BSA) can trigger cellular uptake of TNF. Therefore we tested the hypothesis that MGO-modified proteins may cause TNFalpha secretion in

macrophage-like RAW 264.7 cells. Treatment of cells with MGO-BSA induced TNFalpha release in a dose-dependent manner. MGO-modified ribonuclease A and chicken egg ovalbumin had similar effects. Cotreatment of cells with antioxidant reagent N-acetylcysteine (NAC) inhibited MGO-BSA-induced TNFalpha secretion. MGO-BSA stimulated the simultaneous activation of p44/42 and p38 mitogen-activated protein kinase. PD98059, a selective MEK inhibitor, inhibited MGO-BSA-induced TNFalpha release as well as ERK phosphorylation. Pretreatment of cells with NAC also resulted in inhibition of MGO-BSA-induced ERK phosphorylation. MGO-BSA induced dose-dependent NFkappaB activation as shown by electrophoresis mobility shift assay. The MGO-BSA-induced NFkappaB activation was prevented in the presence of PD98059, NAC, and parthenolide, a selective inhibitor of NFkappaB. Furthermore, the NFkappaB inhibitor parthenolide suppressed MGO-BSA-induced TNFalpha secretion. Confocal microscopy using dichlorofluorescein to demonstrate intracellular reactive oxygen species (ROS) showed that MGO-BSA produced more ROS compared with native BSA. MGO-BSA could also stimulate protein kinase C (PKC) translocation to the cell membrane, considered a key signaling pathway in **diabetes**. However, there was no evidence that PKC was involved in TNFalpha release based on inhibition by calphostin C and staurosporine. Our findings suggest that the presence of chronically elevated levels of MGO-modified bovine serum albumin may contribute to elevated levels of TNFalpha in **diabetes**.

L22 ANSWER 17 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:86411 BIOSIS
DOCUMENT NUMBER: PREV200300086411
TITLE: Are oxidative stress-activated signaling pathways mediators of insulin resistance and beta-cell dysfunction?.
AUTHOR(S): Evans, Joseph L. [Reprint Author]; Goldfine, Ira D.; Maddux, Betty A.; Grodsky, Gerold M.
CORPORATE SOURCE: Medical Research Institute, 444 De Haro St., Suite 209, San Francisco, CA, 94107-2347, USA
jevansphd@earthlink.net
SOURCE: Diabetes, (January 2003) Vol. 52, No. 1, pp. 1-8. print.
ISSN: 0012-1797 (ISSN print).
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Feb 2003
Last Updated on STN: 6 Feb 2003

AB In both type 1 and type 2 **diabetes**, diabetic complications in target organs arise from chronic elevations of glucose. The pathogenic effect of high glucose, possibly in concert with fatty acids, is mediated to a significant extent via increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and subsequent oxidative stress. ROS and RNS directly oxidize and damage DNA, proteins, and lipids. In addition to their ability to directly inflict damage on macromolecules, ROS and RNS indirectly induce damage to tissues by activating a number of cellular stress-sensitive pathways. These pathways include nuclear factor-kappaB, p38 mitogen-activated protein kinase, NH2-terminal Jun kinases/stress-activated protein kinases, hexosamines, and others. In addition, there is evidence that in type 2 **diabetes**, the activation of these same pathways by elevations in glucose and free fatty acid (FFA) levels leads to both insulin resistance and impaired insulin secretion. Therefore, we propose here that the hyperglycemia-induced, and possibly FFA-induced, activation of stress pathways plays a key role in the development of not only the late complications in type 1 and type 2 **diabetes**, but also the

insulin resistance and impaired insulin secretion seen in type 2 **diabetes.**

L22 ANSWER 18 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:574874 BIOSIS
DOCUMENT NUMBER: PREV200200574874
TITLE: p38 and activating transcription factor-2 involvement in osteoblast osmotic response to elevated extracellular glucose.
AUTHOR(S): Zayzafoon, Majd; Botolin, Sergiu; McCabe, Laura R. [Reprint author]
CORPORATE SOURCE: Dept. of Physiology, Michigan State University, 2201 Biomedical and Physical Sciences Bldg., East Lansing, MI, 48824, USA
mccabel@msu.edu
SOURCE: Journal of Biological Chemistry, (October 4, 2002) Vol. 277, No. 40, pp. 37212-37218. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Nov 2002
Last Updated on STN: 7 Nov 2002
AB Poorly controlled or untreated **type I diabetes** mellitus is characterized by hyperglycemia and is associated with decreased bone mass and osteoporosis. We have demonstrated that osteoblasts are sensitive to hyperglycemia-associated osmotic stress and respond to elevated extracellular glucose or mannitol by increasing c-jun and collagen I expression. To determine whether MAPKs are involved in this response, MC3T3-E1 osteoblasts were treated with 16.5 mM glucose, mannitol, or contrast dye for 1 h. Immunoblotting of phosphorylated p38 demonstrated activation of p38 MAPK by hyperosmotic stress in vitro and in vivo. Activation peaked at 20 min, remained detectable after 24 h, and was protein kinase C-independent. Activating transcription factor-2 (ATF-2) activation followed the same pattern as phospho-p38. Transactivation of cAMP response element (CRE)- and c-jun promoter (containing a CRE-like element)-reporter constructs increased following hyperosmotic treatment. SB 203580 (a **p38 MAPK inhibitor**) blocked ATF-2 phosphorylation, CRE transactivation, and c-jun promoter activation. Hyperosmotic activation of collagen I promoter activity was also inhibited by SB 203580, consistent with the involvement of c-jun in collagen I up-regulation. Therefore, we propose that hyperglycemia-induced increases in p38 MAPK activity and ATF-2 phosphorylation contribute to CRE activation and modulation of c-jun and collagen I expression in osteoblasts.

L22 ANSWER 19 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:113519 BIOSIS
DOCUMENT NUMBER: PREV200200113519
TITLE: Heme oxygenase-1 protects pancreatic beta cells from apoptosis caused by various stimuli.
AUTHOR(S): Tobiasch, Edda; Gunther, Lukas; Bach, Fritz H. [Reprint author]
CORPORATE SOURCE: Immunobiology Research Center, Beth Israel Deaconess Medical Center, Harvard Medical School, 99 Brookline Ave, Boston, MA, 02115, USA
fritzhbach@aol.com
SOURCE: Journal of Investigative Medicine, (November, 2001) Vol. 49, No. 6, pp. 566-571. print.

ISSN: 1081-5589.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jan 2002
Last Updated on STN: 26 Feb 2002

AB Background: Several problems can occur after allogeneic islet transplantation: primary nonfunction, rejection, and the recurrence of autoimmune disease, which involve attack by the recipient's cytokines, T cells, natural killer cells, and monocytes on the donor's beta cells, which leads to beta-cell destruction. Recent studies have revealed that loss of transplanted islets is caused mainly by apoptosis. Heme oxygenase-1 (HO-1) is one of the antiapoptotic genes up-regulated under stress conditions. The aim of this work was to investigate any mechanisms of HO-1-mediated protection of beta cells from apoptosis. Methods: Apoptosis was assessed by comparison of viable transfected cells with and without apoptotic stimuli, and with and without HO-1 overexpression. Activation and function of p38 mitogen-activated protein kinase were determined using the specific inhibitor SB203580. Results: We have shown that HO-1 mediates antiapoptotic effects in beta cells. The percentage of apoptotic cells after stimulation with tumor necrosis factor alpha decreased from 75% without HO-1 to 5% when HO-1 was overexpressed. Our data indicate that HO-1 acts as a signal terminator of tumor necrosis factor alpha-induced apoptosis by modulation of the p38 mitogen-activated protein kinase pathway. Conclusions: Profound cell stress that occurs in islets after transplantation, as well as at the onset of **diabetes** , results in beta-cell loss through apoptosis. Protection of beta cells by HO-1 improves their survival in vitro after various proapoptotic stimuli, suggesting that HO-1 suppresses one or several signaling pathways leading to apoptosis. We hypothesize that our in vitro findings can be extrapolated to the in vivo situation, and we propose that expression of HO-1 in islets may illuminate a valuable new approach to improving **diabetes** treatment.

L22 ANSWER 20 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:442256 BIOSIS
DOCUMENT NUMBER: PREV200100442256
TITLE: Activation of renal cortical PI 3-kinase, Akt (PKB) and Erk-1/-2 type MAP kinase but not of p38 MAP kinase, is associated with renal hypertrophy in mice with **type 1 diabetes.**
AUTHOR(S): Faulkner, Jennifer L. [Reprint author]; Gadre, Swarupa [Reprint author]; Senthil, Duraisamy [Reprint author]; Abboud, Hanna E. [Reprint author]; Choudhury, Goutam Ghosh [Reprint author]; Kasinath, Balakuntalam S. [Reprint author]
CORPORATE SOURCE: San Antonio, TX, USA
SOURCE: Diabetes, (June, 2001) Vol. 50, No. Supplement 2, pp. A174. print.
Meeting Info.: 61st Scientific Sessions of the American Diabetes Association. Philadelphia, Pennsylvania, USA. June 22-26, 2001. American Diabetes Association.
CODEN: DIAEAZ. ISSN: 0012-1797.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Sep 2001
Last Updated on STN: 22 Feb 2002

L22 ANSWER 21 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:245222 BIOSIS
DOCUMENT NUMBER: PREV200100245222
TITLE: Hyperglycemia-dependent, agonist-selective impairment of p38 MAPK activation by diabetic PMN.
AUTHOR(S): McManus, L. M. [Reprint author]; Bloodworth, R. C. [Reprint author]; Ghosh, P. M. [Reprint author]; Pinckard, R. N. [Reprint author]
CORPORATE SOURCE: UTHSCSA, San Antonio, TX, 78229, USA
SOURCE: FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A944. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA. March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 23 May 2001
Last Updated on STN: 19 Feb 2002

AB Hyperglycemia-associated infections in **diabetes** reflect a dysfunction in neutrophilic polymorphonuclear leukocytes (PMN). Previously, we observed that PMN from poorly controlled diabetics have reduced functional responsiveness to those agonists which utilize G-protein-coupled receptors (GPCR). The basis for this agonist-selective impairment is unknown but likely reflects altered signal transduction. The present study examined the activation of p38 MAPK in PMN from diabetic (type 1) or normal subjects in relation to glycosylated hemoglobin (HgA1c). Isolated PMN were stimulated with FMLP (100 nM), PAF (1 nM), C5a (10 nM), LTB4 (10 nM), IL-8 (10 nM) or PMA (65 nM); the levels of total or phosphorylated p38 MAPK in cell lysates were determined by Western blotting. Despite the fact that total p38 MAPK was comparable in diabetic and normal PMN, p38 MAPK phosphorylation was markedly reduced in diabetic PMN after stimulation via GPCR. Importantly, this reduction occurred in parallel with a decrease in the level of glycemic control, i.e., as the level of HgA1c was increased, the extent of p38 MAPK activation was decreased. In contrast to the reduction of GPCR-induced p38 MAPK activation in diabetic PMN, the activation of p38 MAPK initiated by PMA was similar to that of normal PMN. This suggests that altered signal transduction in diabetic PMN does not include deficits either at or downstream of PKC activation. In summary, the glycemia-dependent impairment of p38 MAPK activation by diabetic PMN affects diverse agonists which utilize GPCR and likely involves events upstream of PKC activation.

L22 ANSWER 22 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:438872 BIOSIS
DOCUMENT NUMBER: PREV200000438872
TITLE: Expression of the monocyte chemoattractant protein-1 (MCP-1) in rat and human islet cells and in pre-diabetic NOD mice.
AUTHOR(S): Chen, M.-C. [Reprint author]; Proost, P.; Gysemans, C.; Mathieu, C.; Eizirik, D. L. [Reprint author]
CORPORATE SOURCE: Gene Expression Unit, Diabetes Research Center, Vrije Universiteit Brussel, Brussel, Belgium
SOURCE: Diabetologia, (August, 2000) Vol. 43, No. Supplement 1, pp. A76. print.
Meeting Info.: 36th Annual Meeting of the European Association for the Study of Diabetes. Jerusalem, Israel.

September 17-21, 2000. European Association for the Study of Diabetes.
CODEN: DBTGAJ. ISSN: 0012-186X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 18 Oct 2000
Last Updated on STN: 10 Jan 2002

L22 ANSWER 23 OF 23 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002364103 EMBASE
TITLE: p38 and activating transcription factor-2 involvement in osteoblast osmotic response to elevated extracellular glucose.
AUTHOR: Zayzafoon M.; Botolin S.; McCabe L.R.
CORPORATE SOURCE: L.R. McCabe, Dept. of Physiology, Michigan State University, 2201 Biomed./Physical Sciences Bldg., East Lansing, MI 48824, United States. mccabel@msu.edu
SOURCE: Journal of Biological Chemistry, (4 Oct 2002) Vol. 277, No. 40, pp. 37212-37218. .
Refs: 73
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 31 Oct 2002
Last Updated on STN: 31 Oct 2002

AB Poorly controlled or untreated **type I diabetes** mellitus is characterized by hyperglycemia and is associated with decreased bone mass and osteoporosis. We have demonstrated that osteoblasts are sensitive to hyperglycemia-associated osmotic stress and respond to elevated extracellular glucose or mannitol by increasing c-jun and collagen I expression. To determine whether MAPKs are involved in this response, MC3T3-E1 osteoblasts were treated with 16.5 mM glucose, mannitol, or contrast dye for 1 h. Immunoblotting of phosphorylated p38 demonstrated activation of p38 MAPK by hyperosmotic stress in vitro and in vivo. Activation peaked at 20 min, remained detectable after 24 h, and was protein kinase C-independent. Activating transcription factor-2 (ATF-2) activation followed the same pattern as phospho-p38. Transactivation of cAMP response element (CRE)- and c-jun promoter (containing a CRE-like element)-reporter constructs increased following hyperosmotic treatment. SB 203580 (a **p38 MAPK inhibitor**) blocked ATF-2 phosphorylation, CRE transactivation, and c-jun promoter activation. Hyperosmotic activation of collagen I promoter activity was also inhibited by SB 203580, consistent with the involvement of c-jun in collagen I up-regulation. Therefore, we propose that hyperglycemia-induced increases in p38 MAPK activity and ATF-2 phosphorylation contribute to CRE activation and modulation of c-jun and collagen I expression in osteoblasts.